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SULFATHIAZOLE: A CLINICAL AND IN VITRO STUDY OF ITS USE IN INFECTIONS OF THE URINARY TRACT*

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IN the past decade there have been great advances in the treatment of infections of the urinary tract. Before the introduction of sulfanilamide, interest was centered primarily on methenamine and mandelic acid. These urinary antiseptics depended for their action on a certain degree of urinary acidity and the necessary concentration of the bactericidal substance in the urine, but such conditions were difficult to obtain in patients with acute infection, depressed renal function or obstructive lesions of the urinary tract. For these reasons, both drugs were of only limited value. With the introduction of sulfanilamide, reports began to appear concerning its use in urinary-tract infections. It has the advantage of being effective in either an alkaline or an acid urine, provided the concentration is adequate. From the published reports, there is no doubt that sulfanilamide is an effective agent in the treatment of many of these infections.[1-4] Because certain organisms respond slowly, if at all, to this drug, other chemotherapeutic agents were tested.

Fosbinder and Walter[5] recently described several thiazole derivatives of sulfanilamide, the most promising of which appears to be sulfathiazole. Several papers[6-8] have already appeared concerning in vitro studies of these compounds on organisms commonly associated with urinary-tract infections.

This report deals with the study of 25 patients with infections of the urinary tract due to *Escherichia coli, Proteus vulgaris* and *Staphylococcus aureus* who were treated with sulfathiazole; it also discusses comparative studies on the action of various sulfanilamide derivatives on these organisms in vitro. The details of the cases are recorded in Table 1. There were 20 cases of infection due to *Esch. coli,* 3 due to *P. vulgaris* and 2 due to *Staph. aureus.* The primary diagnoses included cystitis, pyelonephritis and perinephritic abscess. The associated lesions included prostatic obstruction, renal stones, megaloureters, pyonephrosis, diabetes mellitus, vesicovaginal fistula, cord bladder and draining cystostomy wounds.

METHOD OF STUDY

To determine the effectiveness of sulfathiazole in the treatment of urinary-tract infections, the following procedures were carried out on each patient. Samples of urine were obtained from women by means of catheterization, and freshly voided specimens were obtained from men. Urine was collected for examination before treatment, two days following the institution of therapy, and at varying intervals thereafter. All cultures of the urine were made within thirty minutes after it was obtained or voided. The organisms were isolated, identified and stored on agar slants. In the specimens of urine containing sulfathiazole, 1 cc. of urine was added immediately to 10 cc. of broth, since the bacteria were soon killed if the urine was allowed to stand. Bacterial counts on urinary sediment were recorded in number of cells per high-power field on both centrifuged and uncentrifuged specimens. The free and total sulfathiazole was determined in the blood and urine after two days' treatment, and at varying periods thereafter. The majority of patients received 2 gm. of sulfathiazole§ by mouth at the beginning of the treatment, followed by 1 gm. every four hours, although some received smaller doses. The total duration of the treatment varied from four to twenty days. The amount of free sulfathiazole

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TABLE 1. *Summary of Data on All Cases.*

CASE NO.	AGE	SEX	DIAGNOSIS	URINE CULTURES*			URINE SEDIMENT†		NO. OF DAYS TREATED	TOTAL SULFATHIAZOLE	SULFATHIAZOLE LEVELS‡				REMARKS
				ORGANISM	POSITIVE	NEGATIVE	BEFORE THERAPY	AFTER THERAPY			BLOOD		URINE		
											Free	Total	Free	Total	
	yr.									gm.	mg./100 cc.	mg./100 cc.	mg./100 cc.	mg./100 cc.	
1	56	F	Acute pyelonephritis and bacteremia	*Esch. coli*	1	3, 8	+	0	7	31	4.8	5.4	364	364	Excellent response
2	47	F	Pyelonephritis	*Esch. coli*	1, 3, 8,		++	++	9	48			182	208	Failure: impacted left ureteral calculus.
3	56	F	Acute pyelonephritis and bacteremia	*Esch. coli*	1, 3	8, 9	++++	+	9	45			143	146	Excellent response; also had auricular fibrillation with congestive failure.
4	27	F	Acute pyelonephritis	*Esch. coli*	1	3, 4, 5, 7	++++	0	7	37	3.4	3.4	177	189	Excellent response; mild diabetes mellitus.
5	58	M	Acute pyelonephritis and cystitis	*Esch. coli*	1, 3		++	+	4	20	5.8	8.3	95	130	Failure; improving until fourth day when patient went into shock following a genitourinary procedure — died in 3 hours.
6	61	F	Chronic pyelonephritis	*Esch. coli*	1	9, 15, 20	+	+	4	21	3.5	5.5	189	245	Improved; temperature never over 99.5°F.; mild diabetes mellitus; nausea and vomiting from drug.
7	77	F	Subacute pyelonephritis	*Esch. coli*	1	4, 7	++	0	6	21	5.9	6.4	400	438	Good response; dysuria and frequency ceased.
8	48	F	Chronic pyelonephritis	*Esch. coli*	1	3, 8, 15	+++	0	11	37	2.8	3.7	255	292	Good response; febrile reaction to drug on 11th day; urinary symptoms relieved; blood pressure 210/125.
9	37	F	Acute pyelonephritis	*Esch. coli*	1, 3, 4, 7, 11, 14		++++	+	7	33	5.5	7.6	214	272	Dramatic clinical recovery; febrile drug reaction on 7th day.
10	68	F	Acute exacerbation of chronic pyelonephritis	*Esch. coli*	3, 9, 11	5, 20	++++	+	14	47	4.6	5.1	101	101	Improved; treated in two courses — relapse followed first, good response followed second.
11	23	F	Acute pyelonephritis	*Esch. coli*	2, 7, 15		++++	+	9	49			201	229	Improved; relapse with febrile and skin reaction to drug on readministration; sulfapyridine and sulfanilamide also tried; severe diabetes mellitus.
12	78	M	Cystitis	*Esch. coli*	6	3, 8	++	+	15	39.5	5.5	7.4	193	297	Good clinical response with symptomatic relief; had prostatic hypertrophy with some obstruction, inguinal hernia, aortic aneurysm and cerebral hemorrhage.
13	21	F	Acute pyelonephritis	*Esch. coli*	1, 3	4, 8, 13	++	0	10	32	4.7	5.1	195	201	Excellent response
14	35	F	Acute pyelonephritis	*Esch. coli*	1	3, 8	+	0	7	29	5.2	5.9	456	532	Excellent response
15	33	F	Acute pyelonephritis	*Esch. coli*	1, 3	3, 6, 8	+	+	8	40	2.0	2.0	46	46	Good clinical response
16	68	M	Acute cystitis	*Esch. coli*	2	4	+++	0	4	15	0.8	1.0	38	73	Good response; postoperative infection.
17	48	F	Acute pyelonephritis	*Esch. coli*	1, 3, 8		++++	0	7	23	0.9	0.9	50	63	Good clinical response
18	60	M	Pyelonephritis, left pyonephrosis and cystitis	*Esch. coli*	1, 3	9, 14, 15, 22	++++	+	20	63	9.7	12.4	222	238	Improved; large, palpable, non-functioning left kidney; urine almost pure pus on entry; had low-grade fever.
19	40	F	Acute pyelonephritis	*Esch. coli*	1, 4	8, 9	++	+	9	33	2.7	2.9	131	151	Good response
20		M	Cystitis	*Esch. coli*	1, 3	6, 8	++++	+++	10	27	3.0	3.1	219	241	Improved; prostatic hypertrophy with obstruction necessitating in-lying catheter; fever subsided.
21	38	M	Perinephritic abscess	*Staph. aureus*	1	3	+	0	7	40	3.6	3.9	288	300	Temperature did not fall until perinephritic abscess was drained
22	59	F	Pyonephrosis, megaloureters and septic lung infarct	*Staph. aureus*	6	2, 10	++++	++	13	23.5			32	32	Sputum culture: *Staph. aureus*; relapse following first course; nausea and vomiting from drug.
23	58	M	Pyelocystitis and multiple septic lung infarcts	*P. vulgaris*	1, 23	6, 16			18	69	5.6	7.2	310	420	Ruptured suprapubic cystostomy wound; multiple lung abscesses, with *P. vulgaris* in sputum; cultures became negative and fever lower under treatment.
24	70	F	Cystitis and vesicovaginal fistula	*P. vulgaris*	1	7	++++	+	7	10.5					Excellent response; signs of local irritation relieved for first time.
25	16	F	Cystitis and cord bladder	*P. vulgaris*	1	2, 4, 9, 11, 15, 19	+++	0	8	17	7.6	9.0	222	225	Excellent response; failed on sulfanilamide therapy.

*The numbers indicate the hospital days on which the cultures were taken.

†0 = no white blood cells per high-power field; + = 1–5 cells; ++ = 5–25 cells; +++ = 25–50 cells; ++++ = more than 50 cells.

‡On the second hospital day.

in the blood varied from 0.8 to 9.7 mg. per 100 cc., and the concentration in the urine varied from 32 to 456 mg. per 100 cc.

In vitro studies were carried out, using as culture mediums the urine obtained before therapy and after two days of treatment. After the pH of these two samples had been adjusted to 6.5 or 7.0, they were passed through a Berkefeld filter and stored in an icebox until used. One cubic centimeter of a saline dilution of a twelve-hour broth culture of the organism originally isolated from the same patient was added to 10 cc. of the two samples of urine. The tubes were then incubated at 37°C., pour plates were made from the culture at four, eight, twelve and twenty-four hours, and the colonies were counted. Each experiment was set up so that a small inoculum of 10 to 100 organisms per cubic centimeter and a large inoculum of 1000 to 100,000 organisms per cubic centimeter were used.

Results of Clinical Study

Escherichia coli *Infections*

Of 20 cases of *Esch. coli* infection 13 were cured, 5 were improved, and in 2 the treatment failed to influence appreciably the course of the disease. All the uncomplicated cases made a dramatic clinical recovery, with disappearance of symptoms and a fall of temperature to normal within two to four days. In 2 (Cases 9 and 17) the cultures remained positive but relapses did not occur during the ensuing month.

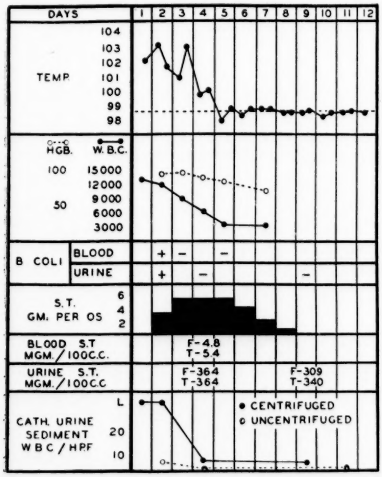

Figure 1. *Pyelitis, with Bacteremia (Case 1).*

The details of Case 1 are shown in Figure 1; they are illustrative of the response seen in the cases classified as cured. This fifty-six-year-old woman entered with a history of dysuria of three weeks' duration. On admission she had a chill, *Esch. coli* was recovered from the blood and urine, and there was pyuria. The response to sulfathiazole therapy was dramatic, and subjective improvement was noted within twenty-four hours. Figure 2 *A* shows the marked bactericidal effect of this patient's urine, during therapy, for the organism isolated before the onset of treatment. Here 10,000 organisms per cubic centimeter of urine were killed within twenty-four hours, whereas the organisms grew freely in the urine containing no sulfathiazole. This is the type of growth curve obtained for the majority of the patients with *Esch. coli* infections when the urine is studied before and during treatment with sulfathiazole.

The 5 cases classified as improved had the following complications. In Case 6 the patient had diabetes as well as chronic pyelonephritis. Sulfathiazole had to be discontinued after four days because of nausea and vomiting. Although the symptoms of infection were relieved and the urine became sterile, the patient continued to run a low-grade fever. In Case 11 the patient, who also had a severe diabetes, was apparently cured but relapsed after therapy was discontinued, and on readministration of sulfathiazole developed fever and a cutaneous reaction. In Case 10 there was a relapse after five days of treatment but the patient responded promptly to a second course. Initially the patient was probably insufficiently treated. In Case 20 there was a prostatic obstruction and an inlying catheter was used. The cultures became sterile and fever subsided, but pyuria continued. In Case 18 a sixty-year-old man had a large, palpable, nonfunctioning left kidney; the urine became clear and sterile and dysuria was relieved, but the low-grade fever continued.

Two cases were classified as failures. In one (Case 2) there was a calculus in the left ureter, and under treatment the patient continued to show fever and bacilluria. In the other (Case 5) the patient developed shock and died following a genitourinary procedure.

Proteus vulgaris *Infections*

There were 3 cases of *P. vulgaris* infection, 2 of which showed an immediate favorable response following the use of the drug (see below). The third (Case 23) was seen following a one-stage prostatectomy; the patient had not only suprapubic drainage of the bladder but also multiple lung abscesses. *P. vulgaris* was isolated in almost pure culture from both the urine and the sputum.

While the patient was receiving sulfathiazole, the urine cultures became negative and there was clinical improvement. The drug treatment was discontinued when the patient left our care, and *P. vulgaris* promptly reappeared in the urine draining from the suprapubic wound.

Figure 3 illustrates the clinical course of a sixteen-year-old girl (Case 25) who was seen at the Evans Memorial Hospital. On entry she was found to have an atonic bladder, flaccid paralysis of the left arm and leg, flaccid paresis of the right leg and a left-sided Horner's syndrome. An etiologic diagnosis could not be definitely established, but there was thought to be a widespread vascular lesion of the spinal cord. The patient was placed on tidal drainage of the bladder for forty-four days, after which she regained normal function of the bladder. She had some dysuria and occasional bouts of low-grade fever. Eleven specimens of urine were positive for *P. vulgaris* and contained many leukocytes. She was given two courses of sulfanilamide, without apparent benefit. Two days after the beginning of sulfathiazole therapy the urine was sterilized, and it remained sterile. Figure 4 *A* demonstrates the results of the in vitro action of this patient's urine collected before and two days after treatment was started. Here, with an original inoculum even as large as 100,000 organisms per cubic centimeter there was marked bacteriostasis. The concentration of free sulfathiazole was 222 mg. per 100 cc. of urine.

The other patient (Case 24), whose case was especially interesting because of a long history of infection and recovery after small doses of sulfathiazole, was followed through the courtesy of Dr. Maurice Strauss. She was seventy years old, and had a vesicovaginal fistula, and a *P. vulgaris* infection of the bladder of six months' duration. The symptoms were due to spasm and local irritation of the bladder. She was given 0.5 gm. three times daily. Examination at the end of seven days showed that all local signs of irritation had disappeared and that symptoms were relieved for the first time in many months. The urine culture became negative for *P. vulgaris*.

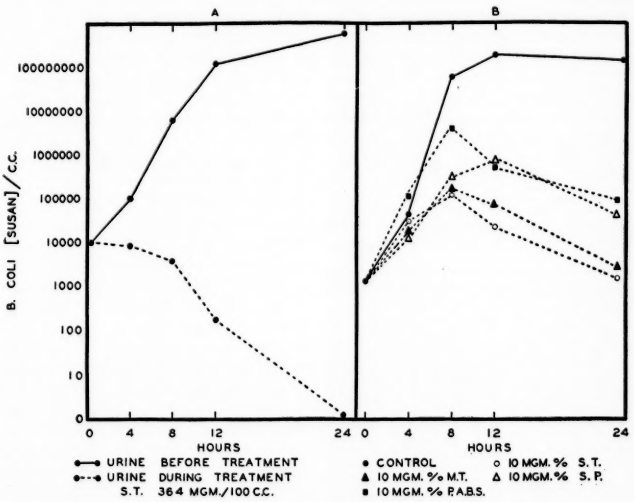

FIGURE 2. *Growth Curve of* Escherichia (Bacillus) coli *in Urine (Case 1).*
S.T. = *sulfathiazole;* M.T. = *sulfamethylthiazole;* S.P. = *sulfapyridine;* P.A.B.S. = *sulfanilamide.*

Staphylococcus aureus *Infections*

Two cases of *Staph. aureus* infection of the urinary tract were treated. In Case 21 the urine became sterile under therapy; the fever persisted, however, and the patient developed signs of perinephritic abscess. Drainage at operation was fol-

lowed by complete recovery. The course was uninfluenced in Case 22. As can be seen from the table, the patient had pyonephrosis, megaloureters and a lung abscess. Both cases demonstrate the fact that if response to drug therapy is not obtained some complicating factor is usually present. That the urine becomes bactericidal is clearly demonstrated in Figure 5 A (Case 21). The urine showed complete sterilization at the end of twenty-four hours' incubation.

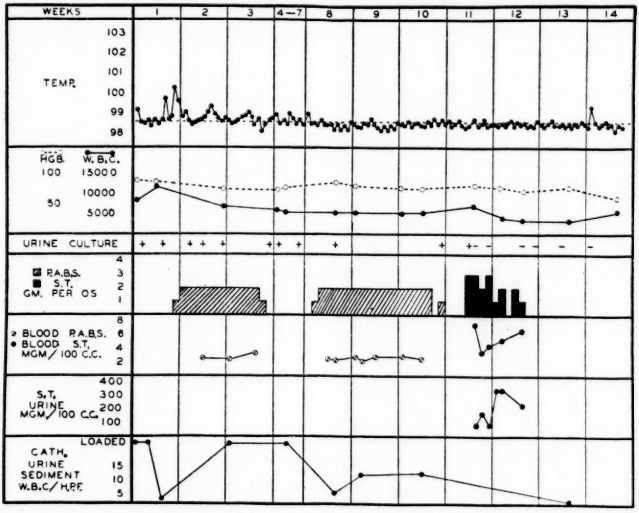

FIGURE 3. *Cystitis Due to* Proteus vulgaris *(Case 25).*

COMPARATIVE STUDY OF SULFANILAMIDE DERIVATIVES IN URINE

To justify a report on the use of a new drug, namely, sulfathiazole, it was believed that a comparative study of the sulfanilamide derivatives in vitro was necessary. The experiments reported here were all done on the same sample of urine, which had been adjusted to a pH of 7.0. Sulfanilamide, sulfapyridine, sulfamethylthiazole* and sulfathiazole were added, so that the final concentration was 10 mg. per 100 cc. Growth curves were then determined following a technic similar to that described above.

Various strains of *Esch. coli* that had recently been isolated from patients with urinary-tract infections were used in these experiments. Figure 6 *A* shows a typical example of one of the growth curves. In both the control and the drug-containing tubes there was an initial growth period of about four hours, following which the effect of the various drugs became manifest. The urine containing sulfanilamide showed moderate bacteriostasis, but that containing sulfapyridine showed it to a more marked degree. Urines containing sulfathiazole and sulfamethylthiazole both exhibited bactericidal as well as bacteriostatic action. Usually sulfathiazole was a little more effective than sulfamethylthiazole; however, the difference was not striking.

Occasionally some strains of *Esch. coli* appeared to be somewhat more resistant to the action of these drugs. Figure 2 *B* is an example. Here, although the original inoculum was larger than that in Figure 6 *A*, the action was not so marked as that generally observed. However, urine containing sulfathiazole again showed the most marked bacteriostasis. Not infrequently, *Aerobacter aerogenes* is found to be the infecting organism in urinary-tract infections. Figure 6 *B* shows the comparative action of the drugs on this organism, which had recently been isolated from the blood stream of a patient with urinary-tract infection. In this experiment the action of sulfathiazole was striking.

Sulfanilamide therapy in *P. vulgaris* infections of

*Supplied through the courtesy of the Winthrop Chemical Company, New York City.

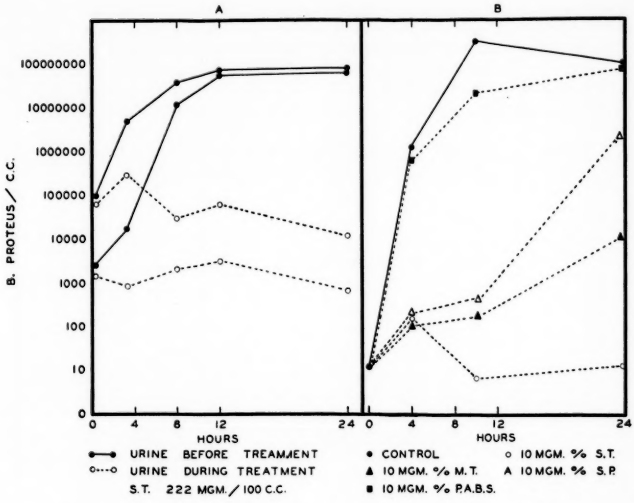

FIGURE 4. *Growth Curve of* Proteus vulgaris (B. proteus) *in Urine (Case 25).*

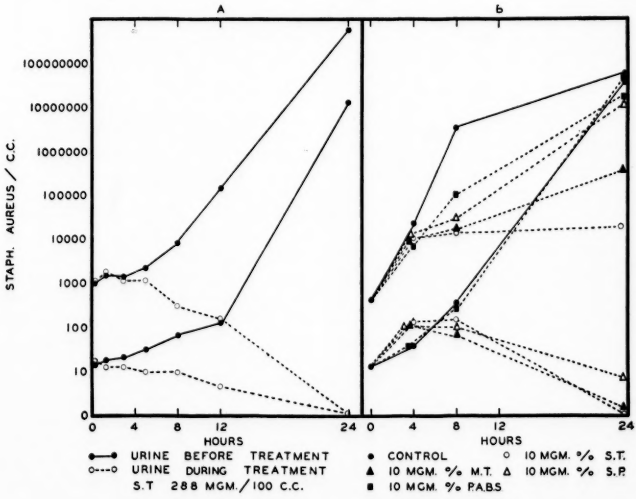

FIGURE 5. *Growth Curve of* Staphylococcus aureus *in Urine (Case 21).*

the urinary tract has been somewhat disappointing, and the results of a comparative study of the activity of the drugs against this organism are therefore especially interesting. Long and Bliss[7] reported some inhibition of growth in broth cultures containing 10 mg. per 100 cc. Figure 4 *B* is an example of the action of sulfathiazole on *P. vulgaris* in urine. When large inoculums were used all tubes showed growth, but some bacteriostatic action could be demonstrated in those con-

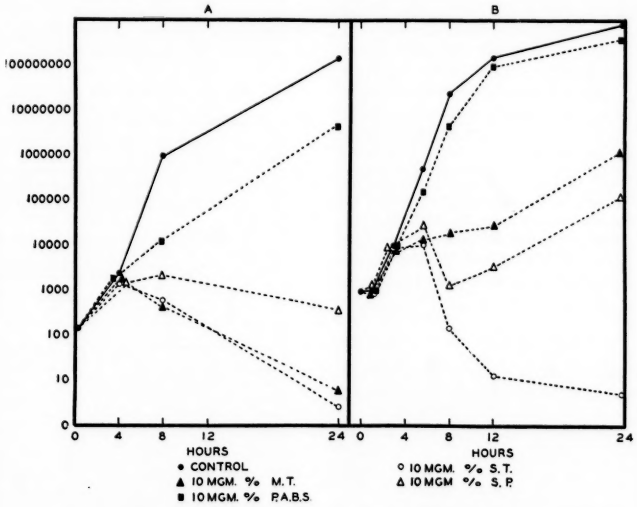

FIGURE 6. *Growth Curves of* Escherichia coli (A) *and* Aerobacter aerogenes (B) *in Urine.*

taining sulfathiazole. Sulfanilamide in this experiment, as well as in others not here reported, had little demonstrable effect. Sulfapyridine appeared to be more effective than sulfanilamide, and sulfathiazole and sulfamethylthiazole the most active of all.

Sulfanilamide and sulfapyridine have been disappointing in the treatment of all staphylococcal infections. Therefore, a drug that is effective against this organism would indeed be most useful. Rammelkamp and Keefer[9] have shown that in whole defibrinated blood sulfathiazole is an effective bactericidal and bacteriostatic agent, even more so than sulfamethylthiazole, sulfapyridine or sulfanilamide. This was also found to be true when urine was used as the medium (Fig. 5 *B*). When a small inoculum was used there was complete sterilization of the urine containing sulfathiazole and sulfamethylthiazole. With a larger inoculum there was bacteriostasis without complete sterilization at the end of twenty-four hours' incubation. Sulfathiazole appeared to be the most effective of the four drugs used against *Staph. aureus.*

DISCUSSION

Sulfathiazole therapy for urinary-tract infections due to *Esch. coli* and *P. vulgaris* has given encouraging results. In this clinical study it has been demonstrated that usually the urine not only becomes sterile and free of leukocytes, but also exhibits definite bacteriostatic and bactericidal action against twenty strains of *Esch. coli,* three strains of *P. vulgaris* and two strains of *Staph. aureus.*

This bacteriostatic and bactericidal action of sulfathiazole was demonstrated in urine containing between 32 and 456 mg. of free sulfathiazole per 100 cc. A favorable response was obtained in three patients (Cases 15, 16 and 17) with a concentration of less than 50 mg. per 100 cc. It appears from these clinical studies and also from studies in vitro that a concentration of between 50 and 200 mg. per 100 cc. of free sulfathiazole is sufficient to sterilize the urine. It is necessary to give 2 to 4 gm. of sulfathiazole in divided doses daily to obtain such concentrations. Restriction of fluid is not neces-

sary. In severe infections, especially those associated with stasis of urine, a concentration of sulfathiazole between 200 and 450 mg. is needed. This amount of the drug in the urine may be obtained by giving 4 to 6 gm. in divided doses daily.

No severe toxic manifestations were encountered in these cases. Nausea and vomiting occurred in two cases, and there were febrile reactions in 3, one accompanied by a cutaneous eruption. The bloods and urines were followed closely, but no evidence of toxic effects was noted.

It is interesting that complicating factors, such as diabetes mellitus, prostatic obstruction, pyonephrosis and nausea and vomiting, were present in the patients not promptly cured. Close analysis shows that some improvement took place under drug therapy, and this treatment seems valuable even in these cases.

In vitro studies on the action of the various sulfonamide compounds in concentrations of 10 mg. per 100 cc. showed that sulfathiazole had the most marked bacteriostatic and bactericidal action. Several experiments with higher concentrations of the drugs showed sulfathiazole to be more effective, even at these concentrations.

Conclusions

Sulfathiazole was used in the treatment of 25 cases of urinary-tract infections, and it was shown to be effective against *Escherichia coli, Proteus vulgaris* and *Staphylococcus aureus* infections.

The urine of patients receiving sulfathiazole exhibited marked bactericidal and bacteriostatic action in vitro.

Comparative studies of the action of sulfathiazole, sulfamethylthiazole, sulfapyridine and sulfanilamide in urine containing 10 mg. per 100 cc. showed that sulfathiazole is the most effective bactericidal and bacteriostatic agent against *Esch. coli, Aerobacter aerogenes, P. vulgaris* and *Staph. aureus.*

Sulfathiazole deserves further clinical trial in the treatment of urinary-tract infections.

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FAMILIAL HEMOLYTIC CRISIS*

Report of Three Cases Occurring Within Ten Days

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BOSTON

WITHIN a period of ten days, three children in the same household — two brothers and a cousin — became successively ill and were admitted to the Waltham Hospital for treatment. Each child was found to be suffering from a severe hemolytic crisis, and splenectomies were performed on all three. The first child died, but the other two made uneventful recoveries. This report is presented because hemolytic crises occurring successively at short intervals in members of the same family are rare, and because the management of these cases is of the utmost importance.

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Case Reports

Family Background. The patients, D. C. M., 2nd, R. M., Jr., and M. McN., were grandchildren of D. C. M. aged 70, a known case of congenital hemolytic icterus, who considered himself to be in good health, was able to do his daily work as a carpenter and had no symptoms. He had never been anemic and had never been subject to sudden attacks of icterus. Examination revealed slight icterus and a large spleen extending three fingerbreadths below the left costal margin. Examination of the blood (Table 1) showed no definite anemia, although reticulocytosis, spherocytosis and increased hypotonic fragility were present. His son, R. M., aged 41, the father of D. C., 2nd, and of R. M., Jr., had been jaundiced since childhood. He was troubled with lack of "pep," occasional spells of vomiting and sporadic attacks of marked jaundice. Examination revealed moderate icterus and an enlarged spleen felt four fingerbreadths below the left costal mar-

gin. Examination of the blood (Table 1) showed high hemoglobin levels and no anemia, although reticulocytosis, spherocytosis and increased hypotonic fragility were present. R. M. had three brothers and a sister. One brother had tuberculosis; the others were well. One sister, who died at 26 of miliary tuberculosis, had been jaundiced for years. Her only child, M. McN., lived with the R. M. family, having been adopted by them. There were probably other cases of hemolytic icterus in the family, which was a large one, but this could not be verified.

TABLE 1. *Data on D. C. M. and R. M.*

	Hemoglobin	Red-Cell Count	White-Cell Count	Platelet Count	Reticulocytes	Mean Corp. Volume	Mean Corp. Diameter	Mean Corp. Thickness	Fragility	Serum Bilirubin
	%	$\times 10^6$	$\times 10^3$	$\times 10^3$	%	*cu. microns*	*microns*	*microns*	*% NaCl*	*mg./100 cc.*
D. C. M.	85	4.34	7.0	269	1.9	90	6.57	2.7	0.60-0.16	3.8
	99	4.94	10.0	547	9.4				0.68-0.22	
R. M.	97	4.53	10.3	440	2.2	90	6.77	2.5	0.68-0.20	
	110	5.32	14.0	1,500	14.2	83	6.70	2.4	0.80-0.04	4.2

CASE 1. D. C. M., 2nd, an 11-year-old boy, had been known to have jaundice, anemia and splenomegaly for years. About three times a year he developed slight attacks of fever, weakness, pallor and increased icterus, but the attacks were always mild and cleared up after a few days' rest at home. On April 13, 1938, he complained of dizziness and pain in the midabdomen and vomited several times. He became rapidly worse on April 14, when well-marked jaundice and pallor were noted. The next day his condition seemed desperate and he was admitted to the Waltham Hospital by Dr. Frank J. Fleming, to whom I am indebted for the privilege of seeing these cases.

Physical examination revealed a small, rather underdeveloped boy lying quietly in bed. He appeared acutely ill, had the appearance of mild shock and showed well-marked pallor, with a lemon-yellow discoloration of the skin and scleras. The temperature ranged between 101 and 103.5°F., and the pulse rate between 120 and 140. A soft systolic murmur was heard at the apex. The spleen was palpable three fingerbreadths below the left costal margin. Examination of the blood showed a red-cell count of 1,250,000, with 36 per cent hemoglobin (Sahli), and a white-cell count of 3800. The red cells showed an extreme degree of spherocytosis, and the average red-cell diameter was 5.63 microns. On April 16, the patient's condition was critical, the red-cell count having dropped to 1,010,000. An emergency splenectomy was decided on. Just prior to operation the patient was given 1000 cc. of normal salt solution and 500 cc. of citrated blood. The operation was performed by Dr. H. Quimby Gallupe without incident. During the operation 600 cc. of blood was given slowly intravenously. In all, 2100 cc. of fluid was given intravenously within 90 minutes. At the end of the operation the patient began to pass large quantities of frothy sputum. All attempts at resuscitation failed, and the patient shortly expired, apparently of pulmonary edema. Permission for autopsy was refused.

CASE 2. R. M., Jr., a 12-year-old boy, like his brother (Case 1), had been known to have hemolytic icterus for years. Several times annually he had mild attacks of fever and malaise, during which an increase in pallor and jaundice was always noted. The present attack, which was much severer than any previous one, began on April 21, 1938, or 8 days after the onset of his brother's crisis. It was characterized by fever, malaise, headache and left-sided abdominal pain. The next day there was marked dizziness and weakness, and the patient was admitted to the Waltham Hospital.

Physical examination revealed an acutely ill child, somewhat small for his age, with extreme pallor and slight

TABLE 2. *Data on R. M., Jr.*

Date	Hemoglobin	Red-Cell Count	White-Cell Count	Platelet Count	Reticulocytes	Mean Corp. Volume	Mean Corp. Diameter	Mean Corp. Thickness	Fragility	Serum Bilirubin
	%	$\times 10^6$	$\times 10^3$	$\times 10^3$	%	*cu. microns*	*microns*	*microns*	*% NaCl*	*mg./100 cc.*
4-22-38	30	1.22	3.0		0.4		6.23		0.64-0.34	5.1
4-23										
1 a.m.: transfusion (500 cc.)										
4 a.m.: transfusion (400 cc.)										
8 a.m.	47	2.54	3.6							
10 a.m.: transfusion (400 cc.)										
12 m.	69	3.66			0.6					
3 p.m.	70	3.33								
4-24										
9 a.m.	68	2.56								
11 a.m.: splenectomy										
1 p.m.: transfusion (500 cc.)										
4-25	93	5.47			0.3					
4-26	89	4.67								
5-6	98	4.64								
5-17	80	3.72	8.3	538	1.3					
6-14	89	4.61		1,200	1.6					
7-12	92	4.56		820	0.2				0.56-0.22	
8-16	99	4.88		1,220	1.0					
10-18	102	5.06	7.3	1,113	1.2	84	6.7	2.3	0.52-0.26	
2-20-39	95	4.83	8.4	740	0.2				0.60-0.04	
4-17-40	93	4.78	8.9	1,061	1.4	90	6.3	2.9	0.56-0.12	0.9

jaundice. The temperature was 103.6°F., the pulse 120, and the blood pressure 104/60. The heart was not enlarged, but a rather loud, blowing systolic murmur was heard over the precordium. A large, somewhat tender spleen was felt three fingerbreadths below the left costal margin. Examination of the blood showed a marked anemia: a red-cell count of 1,220,000, with 30 per cent hemoglobin (Sahli), and an associated leukopenia (Table 2). There was extreme spherocytosis of the red cells, and the hypotonic fragility test showed beginning hemolysis at 0.64 per cent of sodium chloride solution, complete at 0.34 per cent. Because of the fatal result in Case 1, it was decided to give several transfusions prior to splenectomy, but spaced at intervals of at least 3 hours. Transfusions of citrated blood of 400 or 500 cc. each were accordingly given at 1, 4 and 10 a.m., April 23, with the result that at 3 p.m. the hemoglobin had risen to 70 per cent and the erythrocyte count to 3,330,000. On the morning of April 24 the patient looked considerably better, and there was a definite diminution in both the temperature and the pulse rate. However, the hemolytic process was apparently still quite active, as indicated by a drop in the erythrocyte count to 2,560,000 in 15 hours. Splenectomy was performed by Dr. Gallupe under nitrous oxide, oxygen and ether anesthesia, and 2 hours later another transfusion of 500 cc. of citrated blood was given. Sections of the spleen showed marked congestion of the pulp. On the following day, dramatic rises in both hemoglobin and red-cell count were evident. Convalescence was uneventful, the temperature and pulse becoming normal by lysis in 8 days. No further transfusions were necessary. At discharge from the hospital on May 6 the hemoglobin was 98 per cent and the red-cell count 4,640,000 (Table 2). The patient has since been entirely well and has shown a striking increase in weight and stature.

Case 3. M. McN., a 5-year-old girl and the cousin of the two boys (Cases 1 and 2), had also been known to have hemolytic jaundice and had had several attacks of hemolytic crisis. The present attack began on April 22, 1938, the day after the onset in Case 2. There was at first malaise and fever. The next day the patient complained of lower abdominal pain and headache, and on April 24 she was admitted to the Waltham Hospital.

Physical examination revealed a very delicate-looking, acutely ill child with marked pallor and slight icterus. The temperature was 103°F. and the pulse 120. The splenic edge was felt one fingerbreadth below the left costal margin. Examination of the blood showed a red-cell count of 1,700,000, with 35 per cent hemoglobin, and a white-cell count of 5000 (Table 3). There was marked spherocytosis, and the hypotonic fragility test showed beginning hemolysis at 0.80 per cent, with complete hemolysis at 0.56 per cent. Because the patient did not appear so severely ill as her cousins, it was decided to temporize for a day or two. During this period swine serum, prepared by the method recommended by Josephs,[1] was given in increasing dosage for its possible antihemolytic effect. However, by April 26 there was a slight though definite drop in both the hemoglobin level and the red-cell count. Transfusions of citrated blood in 300-cc. amounts were accordingly given on April 26 and 27, and a splenectomy was performed on the latter date by Dr. Gallupe. The spleen weighed 350 gm., and microscopic sections showed marked congestion of the pulp. Convalescence was uneventful. On May 4, the day of discharge, the red-blood cell count was 4,570,000 with 93 per cent hemoglobin, and the white-cell count 10,200. In the course of the next several months there was a definite increase in the diameter of the red cells and a great diminution in spherocytosis but a persistence of abnormal fragility. In April, 1940, spherocytosis was again definitely increased.

TABLE 3. *Data on M. McN.*

DATE	HEMOGLOBIN	RED-CELL COUNT	WHITE-CELL COUNT	PLATELET COUNT	RETICULOCYTES	MEAN CORP. VOLUME	MEAN CORP. DIAMETER	MEAN CORP. THICKNESS	FRAGILITY	SERUM BILIRUBIN
	%	$\times 10^6$	$\times 10^3$	$\times 10^3$	%	*cu. microns*	*microns*	*microns*	*% NaCl*	*mg./100 cc.*
4-24-38	35	1.70	5.0				5.81		0.80-0.56	
4-25										
a.m.	35	1.98	5.6		0.7					
p.m.	31	1.83	5.0							
4-26 Transfusion (300 cc.)	30	1.62			0.8				0.62-0.50	
4-27 Transfusion (300 cc.)										
Splenectomy	38	2.25								
4-28	65	4.11	21.0		0.8					
4-29	69	4.04	17.0		0.3					
4-30	70	4.02			0.3					
5-2	78	4.60			0.3					
5-3	89	4.89			0.2					
5-4	93	4.57			0.4					
5-17	71	3.96			0.2					
6-21	80	4.12	13.6						0.60-0.16	
7-12	78	4.27								
9-13	84	4.57	9.5	1,540	2.3	88	7.0	2.3		
2-20-39	90	4.42		1,580		89			0.68-0.16	
4-17-40	89	4.46	7.4	1,471	3.7	84	6.12	2.8	0.64-0.22	1.07

Discussion

The Hemolytic Crisis

Congenital hemolytic jaundice is a chronic hereditary disease subject to more or less frequent and violent fluctuations in the degree of anemia and icterus, known as hemolytic crises. Most authorities[2–4] consider the disease to be a hereditary dis-

order of red-cell formation in the bone marrow, with the production of small thick erythrocytes (spherocytes) as the salient feature.

The hemolytic crisis is difficult to explain on the basis of a congenital disturbance in blood formation. Its outstanding feature is the great increase in spherocytosis and blood destruction, features that closely resemble the sudden development of unusual hemolysis through the action of various toxic, chemical or immunologic substances. Dameshek and Schwartz[5] showed that all the features of the hemolytic crisis, including the marked spherocytosis and increased fragility, could be imitated in the experimental animal by the injection of hemolytic heterophilic serum. These data indicated that spherocytosis is not necessarily of hereditary origin but may be induced by hemolysins of various types. Furthermore, a group of cases of acquired hemolytic icterus was observed in some of which hemolysins were found in the serum and in which spherocytosis and increased fragility were temporarily present.[6, 7] These cases, which indicated the close relation between the presence of hemolysins, hemolytic anemia and spherocytosis, also established from the clinical standpoint that spherocytosis was not necessarily of congenital origin. The concept was therefore advanced that hemolytic anemia or icterus was caused, not by an intrinsic defect of the marrow, but rather by the action of hemolysins of various types and in varying "doses" on mature red blood cells. Both the crisis of chronic congenital hemolytic jaundice and the sudden appearance of acute hemolytic anemia in a previously healthy person might be explained by a sudden increase in circulating hemolysins (arising from the spleen?), with the resultant development in the mature red cells of spherocytosis and increased fragility. The occurrence of hemolytic crisis in three members of the same household within a period of ten days might be further evidence in favor of an extrinsic rather than an intrinsic cause of the crisis.

The nature of the possible extrinsic cause in the reported cases was not determined. The possibility of an infectious process was thoroughly investigated. None of the children showed any evidence of an infection, although this does not exclude such a possibility. The fever present in each case is common to all severe hemolytic processes, and is therefore not necessarily infectious in origin. There was no evidence of an infectious process in any of the immediate family, nor was there any unusual incidence of "grippe" or some similar condition in the neighborhood. Except for their greater severity the crises were closely similar to previous ones, which, according to the mother, always occurred in the spring or fall. The possibility that the children might be allergic to grasses or ragweed was thereupon investigated, but negative results were obtained. The grounds about the house were searched for plants such as the fava bean, but none were found. No unusual foods had been eaten.

In each case, the blood serum and the splenic-vein blood (at splenectomy) were examined for isohemolysins, according to the technic described by Dameshek and Schwartz.[5] None were found, and no unusual agglutinins of either the so-called "cold" or "auto" type were discovered. Severe transfusion reactions did not occur, and no hemolytic or agglutination reactions were observed in cross-matching the patient's blood serum with various donor red cells.

The only comparable group of cases of hemolytic crisis in the literature is that of Dedichen,[8] reported in 1937. Under the title of "'Holla Disease': Epidemic appearance of anemic crisis in hemolytic icterus," this author reported a strange disease that had successively attacked most of the members of two families living in or near Holla, Norway. In the first family (H.), 4 of the 7 children had been taken ill in November, 1933, with fever, vomiting, pallor and enlargement of the spleen. Nine members of the second family (S.), including the father, successively developed acute hemolytic crises in February and March, 1934. The dates of onset were February 22 and March 1, 6, 8, 10, 14, 17, 19 and 22. The hemoglobin readings varied from 20 to 40 per cent, and the hypotonic fragility was greatly increased in all. There were 2 deaths, one in a nine-year-old child (untreated) and the other in a twenty-year-old girl, apparently because of a transfusion reaction (incorrect typing?). Three patients recovered spontaneously, and 4 recovered after one or two transfusions. The typical features of congenital hemolytic jaundice persisted in all the cases, although the splenic size greatly diminished.

Dedichen believed that the hemolytic crises were probably induced by an infection of the "grippal" type, because one of the children of the S. family, not afflicted with the disease congenital hemolytic icterus, fell ill with typical "grippe" during the same period and did not develop anemia or splenomegaly. This opinion seems logical, especially in view of the large number of persons affected and the successive development of the crises within two to seven days of each other. Blood cultures and tests for serum hemolysins were not performed.

The reduction in leukocytes, thrombocytes and reticulocytes in the cases reported here appears at

first glance somewhat unusual, since in the presence of an acute hemolytic process one would expect to find the evidences of increased regenerative activity on the part of the bone-marrow, that is, leukocytosis, thrombocytosis and reticulocytosis. The lack of these features might conceivably be due to unusual splenic activity. The spleen and the bone marrow may be said to have an antagonistic or reciprocal relation. One may speculate as to whether this relation is due to a hormonal influence of the spleen on the marrow, with the result that the maturation or delivery of cells to the circulation becomes inhibited. In sudden splenic hyperactivity, which Heilmeyer[9] believes is at the basis of the hemolytic crisis, it is possible that the bone marrow may become inhibited, with resultant leukopenia, thrombocytopenia and reticulocytopenia. It is also possible that an obscure ("grippal" or influenzal) infection might somehow activate the spleen in these cases, with the resultant development of a hemolytic crisis.

Treatment of Hemolytic Crisis

From the experience gained both in these and in other cases, it appears that although emergency splenectomy as a therapeutic procedure is occasionally necessitated (Doan et al.[10]), the importance of placing the patient in proper condition for the operation is of primary concern. For the patient in apparent shock with fever and profound anemia, it is essential to replace fluids, electrolytes and blood. This may best be done by transfusions, preferably given slowly and at intervals sufficiently spaced to prevent undue strain on the circulation and the right side of the heart. Two to four transfusions of 500 cc. for an adult, or of 250 to 300 cc. for a child, given at three-hour to six-hour intervals are generally sufficient to obtain a quieter, healthier, less anemic patient, with a circulation that is better able to withstand the strain of splenectomy. The sudden introduction into the circulation of large quantities of fluids and blood preliminary to immediate operation (Case 1) may be distinctly harmful. It is therefore recommended that the immediate emergency be combated by transfusions properly spaced, with or without added parenteral fluids, to be followed by splenectomy within twelve to forty-eight hours, when the patient is relatively afebrile, less anemic and with a slower pulse.

Each hemolytic crisis undoubtedly puts a severe strain on the circulation and is usually followed by a prolonged convalescence. Children having frequent crises are generally underdeveloped. The possibility is present, too, that a crisis may be so fulminating as to result in death or in the necessity for an emergency splenectomy. In a very severe crisis, as in the present cases, the operation of splenectomy is probably best not set aside, since the hemolytic tendency may continue to manifest itself as soon as the effects of transfusions have worn off. For these reasons, any child with congenital hemolytic jaundice who is subject to crisis should have a splenectomy performed, preferably between crises. In the presence of a very severe crisis, it is necessary to operate as soon as the patient has been placed in reasonably good condition by carefully spaced transfusions.

Finally a word about the operation of splenectomy is essential. This operation requires a fundamental knowledge of anatomy, skillful surgery and, at times, speed. Certain surgeons appear to possess the knack of delivering the spleen into the operative wound, clamping the splenic pedicle properly and performing the splenectomy—all with a minimum of trauma and wasted motion. In the very serious situation of emergency splenectomy, it is recommended that a surgeon be selected who has had experience in the technic of the operative procedure, and who is known for his adeptness in handling abdominal tissues.

Summary

The appearance in quick succession of three cases of severe hemolytic crisis in one family necessitated emergency splenectomy in all three. Various clinical and hematological features suggested that the hemolytic crises developed because of some alteration outside the bone marrow, perhaps as the result of splenic activation. The operation of emergency splenectomy requires careful preoperative and operative management.

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REMOVAL OF OVER 1300 FOREIGN BODIES FROM A STOMACH*

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BRATTLEBORO, VERMONT

FOREIGN bodies in the stomach have received attention in the literature for a great many years. This case is reported because, in addition to the interest of an unusual collection of foreign bodies, it presents several unique features.

I have not been able to find in the literature any case on which three gastrotomies have been performed, although Matthews[1] and Cannaday[2] have each reported a patient who underwent two. Other unusual features of this case are the great variety of sharp metallic foreign bodies and the large amount of broken glass ingested without acute perforation of the stomach or the intestines. The third unusual feature, the presence of an enormous benign ulcer that had eroded through the gastric wall, has been noted in a previous report.[3] Chalk and Foucar,[4] Gaylord[5] and Wardell[6] are among the few who have recorded a recovery following the removal of heavier or more numerous objects than those in the case reported below. Other cases have been reviewed by Thorek.[7]

FIGURE 1. *X-Ray Film Taken before the Second Operation.*

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CASE REPORT

B. T., a 43-year-old former railroad telegrapher, was a mental patient at the Brattleboro Retreat, where he had been committed for the second time, with a diagnosis of manic depressive psychosis, depressive phase. For several months he had been vomiting occasionally, with increasing frequency. There was coffee-grounds vomitus, with the occasional appearance of bright-red blood. The stools were tarry. Careful observation of the patient led the attendants to believe that he was swallowing foreign bodies. X-ray examination on October 10, 1933, at the Brattleboro Memorial Hospital revealed a large, irregular, opaque mass in the cardiac region of the stomach, measuring about 8 by 10 cm., that appeared to be made up of metal, including staples, tacks and wire. Staples and tacks were visualized in the colon on the right side of the abdomen, some of which appeared in the stools following catharsis. On October 19 x-ray films showed the gastric mass still present and, in addition, 2 small pieces of metal in the ileum and a short piece of wire in the rectum. The patient was referred for immediate operative treatment, since the vomiting and gastric pain persisted and the general physical condition was becoming steadily poorer.

The patient was very anxious for relief and, contrary to his early denials, freely told of the foreign bodies he had swallowed during a period of 3 or 4 months. Before operation he prepared a partial list of these objects so that they "might not be overlooked." He had covered many of the objects, such as razor blades, needles, pins and glass, with chewing gum or food. He said that, in spite of these precautions, his throat had become very sore at times. He admitted that he had intended to commit suicide, but death in this manner became so uncomfortable that he changed to become a very co-operative patient.

Physical examination showed a moderately emaciated and pale, neurotic patient in some distress from epigastric pain. There was tenderness to pressure in the epigastrium. Other physical findings were normal.

Gastrotomy performed on October 20 revealed a large stomach, with the omentum adherent to the lower third of the lesser curvature. The stomach was opened through a transverse incision opposite this point. Numerous intermingled foreign bodies were removed with forceps and fingers. The entire gastric mucosa, especially that along the lesser curvature, was badly lacerated and friable. The omentum, adherent to the lesser curvature, covered the bed of an ulcer, 4.5 by 3.2 cm., that had eroded through the gastric wall. The tissue immediately surrounding the ulcer was extremely friable. The original gastric incision was extended to permit resection of the ulcer. Closure was made, leaving a drain in the lesser omental cavity because of the friable gastric wall. The pathological report was gastric ulcer.

Classification of the foreign bodies removed showed 69 narrow staples, 24 wide staples, 21 pieces of glass, 1 pen-

cil lead, 72 miscellaneous metallic foreign bodies, including open safety pins, hairpins, corroded needles, pins, tacks, pieces of safety razor blade, a piece of hacksaw blade and a screw. The total of 187 foreign bodies weighed 97 gm. In addition, 2 small nails, 2 staples and 2 pieces of glass in the intestines were later delivered by enemas.

A gastric fistula opened through the drainage on the 7th postoperative day and closed spontaneously on the 20th postoperative day; it never gave further trouble. The remainder of the wound healed by first intention. The early convalescence was stormy.

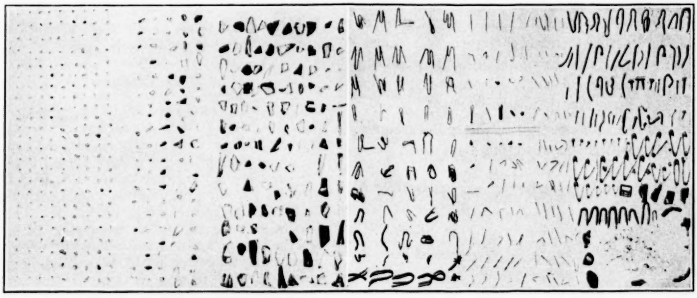

FIGURE 2. *Foreign Bodies Removed at the Second Operation.*

FIGURE 3. *X-Ray Film Taken before the Third Operation.*

The patient was discharged to the Brattleboro Retreat on his 25th postoperative day. Soon he suffered recurrence of pain typical of gastric ulceration. He denied having ingested additional foreign bodies. A modified Sippy regime was ineffective. The patient was suffering severely and was losing weight and strength. At this time he was despondent and attempted suicide. As a last resort he was placed on a course of Synodal. Coincident with the last treatment, he became free of pain and began to gain weight.

Up to 1938 the patient remained in good health and was free of pain. He took advantage of the liberty given him, with the result that, in July, 1938, 5 years after the first operation, he again complained of pain, had tarry stools, occasionally vomited and admitted having taken foreign bodies. X-ray examination showed opaque bodies in the stomach (Fig. 1). On July 15, a second gastrotomy through a 15-cm. incision of the anterior wall of the stomach revealed a mass of broken glass and a tangle of sharp pointed metallic bodies, surrounded by a semiclear, blackish fluid. The strong odor of the action of hydrochloric acid on iron was very evident. A handful of glass was removed at one time from the cardiac portion of the stomach. Many foreign bodies, including open safety pins, had to be untangled and removed individually. In the distal end of the stomach there was an ulcer large enough to admit the tip of a finger. This had a gray base, had not eroded through the gastric wall and was not disturbed. The gastric mucosa, except for one small area, was in good condition, in marked contrast to its friable condition 5 years previously. Perhaps the absence of razor blades accounted for this. The convalescence was uneventful. Complete laboratory studies were not available at this time, but a gastric analysis after operation showed tremendously high levels of acidity: free hydrochloric acid, 280 units; total acidity, 400 units.

Examination of the material removed showed over 440 pieces of glass and 277 metallic bodies, including wire, pins, needles, open safety pins, nails, a bottle cap and a few fragments from a barbed-wire fence, probably collected on his parole home to the farm. For some reason the patient had not swallowed razor blades this time. The weight of the foreign bodies was 551 gm.

Following the second operation the patient was given less liberty, in spite of which, during the following year, he was found to be ingesting other articles. He complained of some stomach distress, and x-ray films were ordered. These showed more foreign bodies (Fig. 3). Physically the patient was in excellent condition. The only abnormality was a fullness of the left midabdomen, which

gave forth metallic sounds on palpation. On May 4, 1939, the patient was again operated on in the surgical department of the Brattleboro Retreat, under Avertin anesthesia. An upper-left-rectus incision was used. Adhesions about the stomach were extensive. The mucosa showed little evidence of injury and was not friable. There was a small ulcer near the pylorus, which was not disturbed. A section of the gastric wall removed at this time was examined by Dr. Arthur Wright, of Albany, New York, who reported as follows:

The mucosa is focally hemorrhagic and subacutely inflamed. The submucosa is diffusely hemorrhagic, edematous and moderately inflamed. Strands of fibrin are present in the interstitial fluid of the submucosa. Diagnosis: mild subacute and acute hemorrhagic gastritis.

FIGURE 4. *Foreign Bodies Removed at Third Operation.*

As previously, the stomach contents were extremely tangled. Removal of this mass of sharp metal and glass was hazardous to the hand within the stomach. Much care had to be taken not to tear the stomach wall while removing pins and needles.

Examination of the material recovered at the third gastrotomy, nearly 6 years subsequent to the first, showed over 425 foreign bodies, including wire, pins, tooth-paste tubes, glass, tacks and so forth (Fig. 4). A nail file was recovered in 3 pieces. The total weight was 295 gm. The convalescence was uneventful.

In the three gastrotomies, 1329 foreign bodies, with a total weight of 943 gm., were successfully removed.

At present the patient is not ingesting foreign bodies so far as is known. He is quite stable mentally and has just been released on parole. He states that he feels in perfect health and denies eating other than a normal diet.

SUMMARY

A case is reported in which, at three operations, over a period of six years, more than 1300 foreign bodies, weighing nearly 950 gm., were removed from the stomach.

4 Elliot Street

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DISCUSSION

DR. ARTHUR W. ALLEN, Boston: Dr. Wheeler's case made exactly the same impression on me that it obviously has made on you. I have had no such experience as this in dealing with foreign bodies in the stomach. I do not mean to imply that in Massachusetts there is a lower percentage of mentally unstable persons than in Vermont, but for some reason or other I have not encountered anyone with such an extreme craving for a metallic diet.

There are certain interesting features of this case that I should like to mention. One is that this is the highest gastric acidity I have ever seen recorded. One wonders whether the high acidity had any bearing on the patient's desire for such a diet, or whether the presence of the foreign bodies had an influence on the activity of the acid cells.

A striking fact concerning traumatic ulcer is brought out. Dr. Wheeler very properly excised the enormous ulceration in the first operation, since it was perforating, but in the second and third, he left the benign ulcers alone. In spite of the very high gastric acidity, this patient apparently had no further trouble from peptic ulcer after the foreign bodies were removed. This is at least some evidence that there are other factors in the development of peptic ulcer than trauma and acidity, although acidity is necessary in the production of any experimental ulcer.

In addition to the psychopathic patient who swallows foreign bodies, there are certain normal people who accidentally get into similar difficulties. One of the most interesting cases of this sort that has come under my care was that of a middle-aged woman who was admitted to the hospital having had periodic attacks of complete pyloric obstruction. The x-ray examinations were slightly confusing in that there seemed to be a shadow, or possibly two shadows, in the stomach that resembled a polyp. These shadows shifted from one portion of the stomach to another. Dr. Edward Benedict examined the patient gastroscopically and saw two foreign bodies that looked to him like the pits of peaches or prunes. I performed a gastrotomy and removed two good-sized peach pits, one of which was quite smooth. The symptoms were doubtlessly due to the occasional engagement of one of these foreign bodies in the pyloric ring. The patient had no recollection of having swallowed these stones.

I believe that one of the earliest gastrotomies for foreign body at the Massachusetts General Hospital was done by Dr. Maurice Richardson, when he operated on a man who had inadvertently swallowed his false teeth.

STRUMA LYMPHOMATOSA

Report of a Case Complicated by Myxedema

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STRUMA LYMPHOMATOSA (Hashimoto's disease) is a lymphoid goiter characterized by a growth of lymphatic elements and the formation of lymphoid follicles, together with certain changes both in the parenchyma and interstitial tissues of the thyroid gland. The condition was first described by Hashimoto[1] in 1912.

Hashimoto considered this disease a separate entity, not to be confused with Riedel's[2] disease. The essential clinical feature of the latter is a widespread involvement of the extrathyroid tissues in a diffuse sclerosis that appears to originate in part of the thyroid gland.

Very little was reported on this subject until Ewing[3] in 1922 confused the picture by coming to the conclusion, following the study of 4 cases, that Hashimoto had described the earlier and Riedel the later stages of the same disease, which he called a benign granuloma of the thyroid gland. As a result of Ewing's view, no attempt was made in the numerous subsequent reports to distinguish between these two conditions. Even within the last few years several authors have held to this view. The assertion of Renton et al.[4] in 1938 that Riedel's disease is characterized by lymphocytic infiltration with or without giant cells conforms closely to Hashimoto's description and not to Riedel's. Jaffe[5] whose work, published in 1937, was chiefly confined to autopsy material, also supported Ewing by urging that the differences between the two conditions are qualitative only.

Boyden, Coller and Bugher,[6] in 1935, stated: "It is our opinion that the conditions described by Riedel and Hashimoto cannot be differentiated either clinically or pathologically. Furthermore, we do not believe that the process is a distinct entity." Vaux,[7] in 1938, came to the conclusion that Riedel's disease and Hashimoto's disease are stages of the same pathologic condition. Microscopically three stages, which merge into each other, can be distinguished — early, intermediate and late. The pathologic changes are the same in all stages, the degree of change being the varying factor. Eisen[8] in reporting 7 cases of Riedel's struma, 3 of which were of the Hashimoto type, concluded that the two conditions are different morphologic manifestations of the same disease process.

On the other hand, numerous authors have expressed the opinion that the diseases are distinct entities. Graham and McCullagh[9] in 1931 and Graham[10] in 1931 from a review of the literature pointed out that Riedel's disease and struma lymphomatosa are distinct and distinguishable. Graham stated that of the 104 cases reported in the literature, 41 could be accepted as Riedel's disease and 24 as Hashimoto's disease, the remainder coming under the different forms of chronic thyroiditis. As a result of his work, the cases subsequently reported were more clearly differentiated as Hashimoto's or Riedel's disease, although enough confusion still exists to make it difficult to classify some of the cases.

Hashimoto's views were upheld and in part confirmed by Heineke[11] in 1914 and Reist[12] in 1922. Williamson and Pearse[13] in 1925, and again in 1929, described the same condition under the name of lymphadenoid goiter. Hellwig[14] in 1938, Clute, Eckerson and Warren[15] in 1935, Mallory[16] in 1935 and 1936, Emerson[17] in 1935, Gilchrist[18] in 1935, McClintock and Wright[19] in 1937, Lee and McGrath[20] in 1937, Lee[21] in 1935, Poer, Davison and Bishop[22] in 1936 are also in essential agreement.

However, the apparent confusion still exists. When Perman and Wahlgren[23] in 1927 tried to prove their view in reporting a case of true Riedel's disease, they were able to show that specimens of pathologic tissue removed at two operations a year apart were of almost identical histologic structure, thus refuting the view that in the early stages of Riedel's disease the histologic findings correspond to what Hashimoto described.

Opposed was a parallel case published by Heyd[24] in 1929, in which the material removed at the first operation was typical of Hashimoto's disease, whereas a section removed thirteen months later showed an increased fibrosis, suggesting an approach to Riedel's disease.

It is obvious that more work and experience with cases of these diseases are needed to clarify the existing opinions.

Joll,[25] who has published the most recent work on the two conditions, whose thorough survey of the literature is excellent and whose personal experience is greater than that of any other person, — he has had 51 cases in his private prac-

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tice and the communicated knowledge of 30 unpublished ones, — is thoroughly in accord with the belief that the diseases are two different entities. His views should be given preference until other investigators have collected as great a number of cases or can in other ways disprove his findings.

Hashimoto claimed that the disease rarely occurred before the age of forty; this age incidence was confirmed by Joll, although the latter knew of a case in a girl of ten. A few cases between the ages of twenty and forty are recorded in the literature. In Riedel's disease, the highest incidence occurs earlier in life, that is, between the ages of twenty-five and thirty-five. In the cases so far reported, there is a marked preponderance of women among patients with Hashimoto's disease, whereas almost the reverse is true in Riedel's disease.

Joll has thoroughly reviewed the pathologic anatomy and histological studies, so that they do not require repetition. Although numerous views have been expressed, the etiology of these diseases remains unknown.

Several recent authors differ as to whether these cases can be diagnosed clinically. Joll believes that once the problem has resolved itself into a differential diagnosis of Hashimoto's and Riedel's diseases, a diagnosis can be made. He states:

> A firm goitre which appears in a middle-aged patient, usually a woman, reaches its maximum in a few months, and involves every part of the gland, causes only a moderate degree of dyspnoea, but produces neither serious pressure effects, thyrotoxic symptoms, pain, tenderness, pyrexia nor other inflammatory phenomena, is almost certainly a struma lymphomatosa. If to these features be added *absence* of any evidence of involvement of extrathyroid tissues and *presence* of some degree of hypothyroidism, the diagnosis is placed beyond a peradventure.

Boyden et al.[6] state, "Positive clinical diagnosis of the condition is practically impossible either before or at the time of the operation, and one must depend on the pathologist to rule out malignancy, especially when clinical findings suggest Riedel's disease." Clute et al.[15] remark, "It is believed that rarely, if ever, can a diagnosis of struma lymphomatosa be made from clinical examination." Graham,[9, 10] on the other hand, believes that a clinical diagnosis should be made on clinical and gross findings, but that a preoperative diagnosis in cases of hyperthyroidism is impossible.

The following listing of characteristic findings is taken from Joll[25]:

Hashimoto's Struma	Riedel's Disease
It preponderates in women from forty-five to sixty years of age.	It occurs in younger men and women than does struma lymphomatosa.
There is a tendency to myxedema.	There is little tendency to myxedema except after radical operation.
All parts of the thyroid gland are involved, but nothing outside. The goiter is sometimes large but never woody hard.	The disease is usually unilateral with extension to extrathyroid structures. The goiter is small, intensely hard and smooth.
Pressure effects are seldom severe.	Grave pressure effects are the rule.
The histologic structure, which varies with the stage of the disease, is characteristic.	The mass is formed of dense scar tissue.

Nearly all authors agree that surgical intervention in cases of struma lymphomatosa is contraindicated, especially in those associated with any signs of hypothyroidism. It is justified only in cases associated with hyperthyroidism; even then, they hold, only enough of the gland should be removed to relieve pressure symptoms or to establish a diagnosis, thus ruling out cancer. All are agreed that myxedema develops in over 50 to 60 per cent of cases, and that following operation this is in most cases brought on much earlier. If struma lymphomatosa is diagnosed and not treated, the basal metabolism rate should be determined frequently to detect the onset of myxedema. Whenever signs of hypothyroidism are evident, thyroid medication should be instituted.

Renton et al.[4] have had good results in the treatment of struma lymphomatosa with x-ray and recently with radium therapy. They think that the latter is almost a specific for this type of goiter, and 1 case that they have followed for five years has shown no signs of hypothyroidism.

The following case is interesting in that it occurred in a young woman who was followed clinically for thirteen years.

Case Report

A 26-year-old woman was first seen at a Boston clinic in January, 1926, when she complained of a goiter. She had had this for 3 years and 6 months and had noticed increasing nervousness and a weight loss of 25 pounds. The basal metabolic rate on entry was +41 per cent, the body weight 150 pounds. A subtotal thyroidectomy was performed on January 22, and the specimen was reported to show primary hyperplasia, follicular type. The clinic record states that the patient was markedly improved after operation; by October, 1926, the basal metabolic rate was −4 per cent and the body weight 190 pounds. When she returned to the clinic in April, 1938, she weighed 245 pounds. The blood pressure on two occa-

sions was 134/100 and 158/130, but later fell to 120/70. The basal metabolic rate was −23 per cent.

The patient was placed for 8 days in a Boston hospital, where, after being put on an 800-calorie diet and given diuretics and small doses of amphetamine (Benzedrine), she lost 23 pounds. She felt much improved. She returned to the hospital in May, where she remained for 3 months. The weight was then 236 pounds and the basal metabolic rate −24 per cent. A systolic murmur was noted over the mitral area. A chest examination by fluoroscopy and stereoscopy showed the heart to be enlarged, so that there was a suggestion of rheumatic heart disease with mitral stenosis. The urine continually showed a slight to large amount of albumin. The patient was again placed on an 800-calorie diet and given Salyrgan and small doses of thyroid. About 10 days after admission jaundice was noted and there was marked tenderness under the costal margin. Duodenal drainage showed much pus and bile pigment. The blood bilirubin rose progressively from 1.6 to 19.0 mg. per 100 cc. With dehydration the nonprotein nitrogen rose to 50 mg. per 100 cc. and the patient was drowsy and irritable. When fluids were given she was more edematous, and ordinary diuretics did not cause diuresis. Injections of 50 per cent glucose intravenously, however, did produce a good diuretic effect. A gallop rhythm was noted during this period. X-ray examinations of the skull and of the long bones were negative. An electrocardiogram showed normal rhythm with low voltage and an inverted T_4. By the middle of August, the jaundice had entirely disappeared and there was less abdominal tenderness, but the patient was still quite weak, and cyanotic on the slightest exertion. She continued to be markedly edematous in spite of the use of vitamins, ammonium chloride, potassium chloride, 50 per cent glucose and digitalis. No definite diagnosis was made. The patient was discharged on August 20.

Following discharge the patient remained at home and in bed. One of us (N. S. S.) was called on August 24, when she showed marked edema of the abdomen and lower extremities. The abdomen was redundant and reached the level of the junction of the upper and middle thirds of the thighs. She had become almost anuric, having passed but 120 cc. of urine in 48 hours. Other physical findings were the same as those in the previous hospital entry. The fluids, which had been restricted, were forced, and the patient was treated symptomatically. She began to show marked improvement after the 5th week at home. By November the pitting edema of the extremities had decreased to a point where it was barely noticeable. Edema of the abdomen had markedly receded, so that it barely overlay the inguinal fold. The patient continued, however, to have localized areas of tenderness, chiefly over the abdomen and lower extremities, varying from day to day. By December she was voiding 900 to 1200 cc. of urine, although her intake was limited to 900 cc. Several attacks of jaundice in this interval were transient and cleared up in 4 or 5 days. At about this time the nails became very brittle and the loss of hair of the head became very noticeable. However, the beard increased so that it required shaving.

In the first week in December the patient became mentally upset and disturbed and was very irrational, incoherent and noisy. At this time she was seen by a neuropsychiatrist, who considered the case to be one of beginning beriberi with peripheral neuritis. She had improved considerably by the early part of January, 1939, so that she could help herself in bed; but she began to put on weight again, the abdomen began to enlarge, and the extremities showed a return of pitting edema. On February 13, she was referred to the Joseph H. Pratt Diagnostic Hospital, under the supervision of Dr. S. J. Thannhauser.

Physical examination showed an extraordinarily large young woman lying helpless in bed. The facies suggested myxedema (Fig. 1). She looked pale. The blood pressure was 100/75 (right arm). The skin was markedly roughened, especially over the lower forearms and the backs of the hands, where there was superficial scaling over a reddish mottling. The skin appeared atrophic in these areas. The superficial scaling was seen also over

FIGURE 1.

Note the obesity and the few hairs; the patient shaved every few days.

the lower legs (Fig. 2). There was an obvious beard around the chin and some hair near the breasts. The pubic hair had a male distribution. The pupillary reactions were normal. The scleras appeared clear; the palpebral conjunctivas were pale. The external ocular movements were normal with no lid lag or nystagmus. The fundi showed well-defined disks, and the retinal fields were normal. By confrontation test the visual fields were adequately large and not defective. The teeth were widely spaced. The tongue was well papillated. The size of the heart could not be determined by percussion because of the obesity; the action was rhythmical and rather rapid. A late systolic blowing murmur was heard along the left sternal border and especially well in the pulmonic area. The vascular pulsations in the neck were wide. No other murmurs were heard in the heart. The lungs were normally resonant, and no rales were heard; the breath sounds were of normal character. The abdomen was flabby, broad and table-like in complete relaxation. No liver or spleen could be felt. There were many striae in the lower quadrants of the abdomen, some appearing reddish and others as pale white cicatrices. There was moderate pitting edema of the dependent abdominal wall, which overlay the flanks and pubis. In the fold of this apron there were excoriations, more marked on the left

side. The arms were small compared with the elephantine legs. The fingernails were almost completely white, owing to superimposed transverse white lines.

Laboratory studies gave no helpful data for the diagnosis of the underlying condition. Basal metabolic studies were not satisfactory.

The patient was kept on a 1000-cc. intake; the urinary output varied between 300 and 550 cc. Early in her stay

FIGURE 2.
The legs show edema and superficial scaling.

the drainage of the edema fluid from the legs and thighs was carried out by the use of cannula-like needles, but this was not continued because of the appearance of inflammation in the areas of drainage and a rise in the white-cell count, even in the absence of fever.

A skin biopsy was reported as consistent with scleroderma. Following this there was infection of the biopsy wound and a purulent infection of the tip of the left middle finger, and the patient had fever for the first time. Sulfanilamide — 15 gr. every 4 hours — was therefore started, but its effect could not be followed since the patient was discharged home on the following day. The fever eventually disappeared.

Following discharge the patient became progressively worse, and died about 3 weeks later, or 13 years after she had come under observation.

Autopsy. The body was that of an obese, edematous woman, 155 cm. tall and weighing 180 pounds. The breasts were practically nonexistent because of the lack of breast tissue. There was extreme pitting edema of the ankles, legs and thighs. The face showed a moderate beard on both cheeks and the chin, with a slight tendency to growth of hair on the upper lip. The pubic hair was scanty and triangular in distribution; the axillary hair was normal. Both legs and arms showed considerably more than the usual amount of hair for a woman. There was a well-healed surgical scar, 8 cm. long, extending around the base of the neck. There were large intertriginous erosions in both inguinal regions, due to the sagging of the abdominal wall onto the thighs. There was a 6-by-1-cm. draining sinus in the lateral aspect of the thigh just below the crest of the ilium. The skin of the face showed an extremely fine wrinkling; that of the abdomen and legs was coarser, and was peculiar in that the epidermis seemed to be separated from and wrinkled over the dermis.

Dissection of the thyroid area revealed two small pieces of what was probably the thyroid gland, totaling less than 1 cm. in diameter.

The heart weighed 450 gm. The myocardium was pale and flabby. The coronary arteries and valves were normal.

The liver weighed 2100 gm. It cut with increased resistance, and the cut surface was somewhat yellow. Close examination suggested an exceedingly fine distribution of excess fibrous tissue throughout the liver, but there was no gross scarring. The lobular markings were normal.

The pituitary gland, adrenal glands and ovaries showed no tumors grossly or microscopically.

Microscopically, the peritracheal tissue consists of a dense collagenous scar, with some muscle embedded in it; scattered through the scar are slight remnants of thyroid tissue made up of flat epithelium or Hürthle's cells making a feeble attempt at acinar formation; not more than 15 acini that contain colloid are found. The thyroid tissue is chiefly represented by disorganized masses of Hürthle's cells with lymphocytic infiltration about them

FIGURE 3.
This remnant of the thyroid gland shows a poorly formed acinus and lymphocytic infiltration.

(Fig. 3).* Also embedded in the scar tissue is a normal-appearing parathyroid gland. The heart presents a striking picture throughout most of the section — especially in regions where muscle bundles are transected — of isolation of each muscle bundle by delicate fibrous tissue and edema. About the blood vessels the amount of fibrosis becomes more marked, and in many places the muscle lobules are separated by fatty infiltration. In some areas many fibroblasts, some appearing quite young, are visible.

*These findings are practically identical with those in the thyroid tissue removed in 1926.

Occasional polymorphonuclear cells and lymphocytes are scattered through this delicate, extensive fibrous stroma. Many dilated capillaries, where endothelial walls appear slightly thickened, are present, and many spaces that appear to be widely dilated lymphatics are also in evidence. The liver shows extreme fatty metamorphosis, so that the tissue looks like pure fat except for small patches of liver cells near the portal areas that are relatively normal. The most striking feature is the uniformity of the size of the cytoplasmic vacuoles. Sections of skin are consistent with scleroderma.

A culture of the edema fluid from the left thigh near the incision showed a hemolytic streptococcus.

Summary

A case of struma lymphomatosa (Hashimoto's disease) is reported. The case is of particular interest because the patient was only twenty-six years old when first seen, because the initial symptoms were those of hyperthyroidism, because she developed myxedema during the thirteen years that the case was observed, and because thyroid tissue removed in 1926 could be compared with that obtained at autopsy in 1939.

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LIMITATIONS OF GASTROSCOPY*

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ALTHOUGH fully cognizant of the valuable objective information that can be obtained through the semiflexible gastroscope in intragastric disease, we have nevertheless found that this method of examination, like every other endoscopic one, has distinct limitations. Since these are not sufficiently emphasized in the current literature on gastroscopy, and are therefore probably not well recognized by the medical profession, we believe that to call attention to them is timely and may help in the proper evaluation of the clinical use of the gastroscope.

In 1932 the Wolf-Schindler gastroscope was devised and its practicality demonstrated. Previously, when only rigid gastroscopes were available, there had been a distinct danger of perforation of the esophagus during gastroscopic examination. Moreover, it required considerable skill to introduce the gastroscope with even relative safety and comfort to the patient. The procedure was therefore limited to a small group of experts. All this was changed completely when the semiflexible gastroscope became available. To introduce it requires no unusual skill, and with some experience the examination can be performed expeditiously, safely and without undue discomfort.

In all large medical centers, as well as in many small hospitals, examination through the semiflexible gastroscope is now performed and dependable observations are made. This has resulted in a large and rapidly growing literature on the subject. Three monographs on gastroscopy have been published since 1932: Moutier's[1] in French and Henning's[2] in German were published in 1935, and Schindler's[3] book in English appeared in 1937. Much of this literature is pioneer work; besides contributions to the early descriptions of the technic and of the indications and contraindications of gastroscopy, numerous papers[4-7] have outlined the normal gastroscopic picture and its changes in the presence of disease. The gastroscopic findings

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in such common diseases as gastritis,[8, 9] gastric ulcer[10, 11] and cancer[12–15] have also been described; the differential diagnosis of ulcer and cancer of the stomach as seen through the gastroscope has been discussed and the roentgenographic and gastroscopic evidences of intragastric disease compared.[16, 17]

A perusal of the literature reveals a great deal of enthusiasm among the authors, who record many cases, often checked by roentgen-ray study, surgery or autopsy, wherein this method of examination disclosed otherwise hidden or overlooked disease of the stomach. In a previous contribution we[18] have reported a series of similar cases. However, in that study we called attention to some difficulties in diagnosis and recorded some errors in interpretation. With growing experience in gastroscopy, we became more conscious of the many difficulties of the method, the shortcomings of the instrument and the various limitations of the procedure.

During the last three and a half years we have performed over 800 gastroscopies, every case having been examined and the observations checked by both of us. All cases had at least one gastrointestinal roentgen-ray examination. In all cases the gastroscopic findings were compared with the roentgen-ray films, as the only other method of morphological visualization of the stomach short of an exploratory laparotomy. This has taught us the value of both procedures; and as clinicians who use every method at our disposal to arrive at a correct diagnosis, we are convinced that neither method should supersede the other. On the contrary, they complement one another, and both should be used in cases where intragastric disease exists or is suspected. The range of the gastroscope is extremely limited as compared with that of the roentgen-ray. It can show the appearance of the mucous membrane of the stomach, but it is, of course, completely unsatisfactory in lesions that involve any other portion of the digestive tract. Another limitation is the inability to obtain biopsy specimens; microscopic confirmation of the observed lesion or lesions is thus rendered impossible. Furthermore, even in its limited field the gastroscope is not infallible. Because of constantly changing view caused by both gastric peristalsis and respiratory movements, small localized lesions of the gastric mucosa may be visualized only at variable times during a gastroscopic examination, and may thus be entirely overlooked. Often one of us has readily located a small lesion such as a superficial ulcer or small polyp, whereas the other at the same examination has found it most difficult to confirm the observation. Also, the discovery of changes in the mucous membrane of the stomach does not necessarily mean that the symptoms are caused by such changes. In fact, secondary changes in the gastric mucosa often accompany disease of the duodenum, gall bladder, liver, heart or other organs. Furthermore, the symptoms of hypertrophic gastritis, especially when it is accompanied by fissures or superficial ulcerations, may simulate those of peptic ulcer. However, if a duodenal ulcer is demonstrated roentgenologically and evidence of hypertrophic gastritis is shown by gastroscopy, we believe that the former condition in all likelihood explains the symptoms. On the other hand, the same gastroscopic findings in the absence of a demonstrable ulcer either in the stomach or duodenum probably account for the digestive symptoms. Thus their relation to all the other evidence determines the diagnostic significance of the gastroscopic findings. In other words, only by intelligent co-ordination of all these data in the light of clinical experience and judgment can the errors of diagnosis be minimized.

Lesions of the antrum involving the lesser curvature may not be demonstrated by gastroscopy. The fault is with the gastroscope in use at present, which does not permit the proper visualization of this portion in a certain type of stomach. Unfortunately, this is a very frequent seat of peptic ulcer and early carcinoma, which may thus be overlooked in a gastroscopic examination. The following case is illustrative.

Case 1. E. H., a 59-year-old man, had epigastric pain of 2 years' duration. The pain usually developed 2 hours after meals and was relieved by the intake of food or soda. Coincidentally there were gas and frequent eructations. The bowel movements were regular, and there had never been bloody or tarry stools. Physical examination was essentially negative. Roentgen-ray examination showed in the prepyloric region a constant, irregular, filling defect suspicious of early carcinoma. Gastroscopy revealed evidence of atrophic changes in the mucosa but no demonstrable lesion in the antrum. Because of the suspicious roentgenological findings, the patient was operated on, and an ulcerating lesion on the lesser curvature of the antrum was found and resected; microscopic examination showed it to be benign.

Gastroscopy may fail to demonstrate cancer in cases in which the stomach cannot be properly distended with air, and considerable food residue, which has not been evacuated by the usual procedure, may obstruct the view. At times the differential diagnosis between cancer of the stomach and localized hypertrophic gastritis is extremely difficult or even impossible on a single examination with a gastroscope. Case 2 is cited to demonstrate the latter difficulty.

Case 2. I. O., a 62-year-old man, was admitted to the hospital complaining of abdominal pain and alternating constipation and diarrhea of 4 or 5 months' duration. Dur-

ing this period he had lost 6 pounds in weight, had become weak and had lost his appetite. Physical examination was entirely negative. The chemical constituents and the cells of the blood were within normal limits. The stools contained no occult blood. Roentgen-ray examination raised the question of a scirrhous carcinoma of the stomach. Gastroscopy revealed a mucous membrane that appeared infiltrated and showed large reddened and partially ulcerated ridges. The gastroscopic diagnosis was cancer of the stomach. The patient refused operation and is now, 16 months later, entirely symptom-free; he has gained weight and is able to follow his usual occupation.

Everyone realizes the difficulties of the clinician and the surgeon in differentiating some cases of ulcer of the stomach and ulcerating carcinoma. It was hoped — and as a matter of fact it has been stated in the literature — that this differential diagnosis could always be made by gastroscopy. However, this is not always so in our experience. We have erred in both directions in such cases and do not depend on a single gastroscopic examination; but if the case can be followed by repeated examinations, the diagnosis often becomes obvious. Case 3 illustrates the difficulties that can be encountered.

CASE 3. P. S., a 46-year-old man, was admitted to the hospital complaining of heartburn and belching of 20 years' duration. Two years previously the patient had an episode of melena and syncope. Roentgen-ray examination of the gastrointestinal tract at that time revealed nothing abnormal. One month prior to entry the patient developed epigastric pain associated with belching. He had lost 8 pounds. Physical examination on admission revealed an apprehensive patient with tenderness just below the umbilicus. Gastric analysis revealed no free hydrochloric acid, even after the administration of histamine. A gastrointestinal roentgen-ray examination showed an irregular mass occupying the superior and medial borders of the cardiac end of the stomach. Gastroscopy showed a large, irregular, ulcerating lesion just below the cardioesophageal opening, which was interpreted as being a cancer. At operation a large soft peptic ulcer was found on the anterior wall of the cardia. It was resected and was shown microscopically to be benign.

One of the most trying experiences in performing a gastroscopy is to examine a patient in whom the roentgen-ray examination has demonstrated a definite niche about the upper third of the lesser curvature of the stomach, and still to fail to visualize the lesion; we have had several such experiences. The following case, in which two gastroscopies failed to show the ulcer, is illustrated.

CASE 4. M. A., a 67-year-old man, entered the hospital complaining of epigastric distress that came 1 to 2 hours after meals and was relieved by the ingestion of soda. He had lost 15 pounds in weight and was referred to the hospital because he did not respond to ambulatory ulcer management. Physical examination was essentially negative. Laboratory examination revealed no relevant deviations from normal. X-ray examination showed a large ulcer niche on the lesser curvature. Two gastroscopic examinations showed a diffuse reddening of the entire gastric mucosa and no evidence of an ulcer.

In stomachs examined postoperatively the gastroscope frequently gives decisive information of the presence or absence of gastritis, marginal ulcer and so forth. However, it is an unpleasant experience to have to record the inability to visualize a stoma when roentgen-ray study has demonstrated a well-functioning gastroenterostomy. A marginal ulcer, particularly if it is on the jejunal side of the stoma, may also be overlooked. This is illustrated by the following case.

CASE 5. A. D., a 39-year-old man, had five admissions to the hospital between June, 1934, and July, 1939. A diagnosis of duodenal ulcer was made in 1934, and because of persistent pyloric obstruction a posterior gastroenterostomy was performed. On July 21, 1938, a roentgenological diagnosis of a functioning posterior gastroenterostomy was made. An old duodenal ulcer was also shown, and the question of a marginal ulcer was raised. A gastroscopy performed on July 25 showed greatly enlarged and tortuous rugae. No gastroenterostomy stoma was seen. Eleven months later the patient was readmitted complaining of severe epigastric pain of 3 hours' duration. The abdomen was rigid throughout. There was marked muscle spasm and rebound tenderness. The patient was operated on the same day, and a perforation of a marginal ulcer was found.

In the presence of an hourglass constriction of the stomach the distal portion cannot be visualized. Thus, although the actual constriction can be seen, the underlying disease may often be overlooked.

Besides these limitations certain other conditions prevent a gastroscopy or contraindicate the introduction of the instrument. In our experience, a small percentage of patients are temperamentally unfit to go through with this examination. In such cases, because of the danger to the uncooperative patient as well as possible damage to the gastroscope, the examination cannot be properly performed. Any serious disease, obstructive or otherwise, of the esophagus is a contraindication to gastroscopy. In cases of severe curvature of the spine or arthritis of the cervical spine, it is frequently impossible. Serious cardiac disease and aneurysm of the aortic arch contraindicate the procedure, as does uncontrollable cough or dyspnea, whatever the cause. Gastroscopy is best avoided in peritonitis, perforated ulcers and acute illnesses with fever. We have also refrained from performing it during acute gastric hemorrhage, although others do not consider this a contraindication. In most of these cases morphologic evidence of intragastric disease can be obtained by roentgen-ray examination.

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SUMMARY

One can say that the intelligent co-ordination of roentgen-ray and gastroscopic examinations as the only two clinical methods for the visualization of the stomach will diminish the error in gastric diagnosis. The two procedures are not antagonistic; on the contrary, they are complementary. Whereas roentgenograms give a great deal of morphological information about the stomach and other intra-abdominal organs, the gastroscope is limited in its field of usefulness. Even failure to observe any pathologic lesions or changes within the gastric mucosa does not exclude intragastric disease. On the other hand, when changes are seen through the gastroscope a lesion is undoubtedly present, but the interpretation of the findings may be difficult. The differentiation between a gastric ulcer and an ulcerating carcinoma is not always possible, and in such cases, re-examination after an interval of several days to several weeks may be necessary for a proper diagnosis. Obviously, its accuracy depends to a large extent on the experience of the observer and his ability to co-ordinate the available gastroscopic, roentgen-ray and clinical evidence. Finally, certain conditions outside the stomach may preclude a gastroscopy or may make it inadvisable or even dangerous. In such cases, for the safety of the patient, gastroscopy should be avoided.

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MEDICAL PROGRESS

RADIATION THERAPY IN GYNECOLOGY

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RADIUM and x-ray treatment are used so extensively in gynecology that a review of their uses and purposes seems called for. Radium and the short-wave lengths of the x-ray both act on tissue in much the same way. They are never stimulating but always destructive. They act to inhibit activity of glandular structures, to inhibit mitoses in malignant growths and ultimately to cause fibrosis of tissue and arteriosclerosis. There has been much written about stimulating doses, but it is likely that radiation releases inhibiting influences and that normal function follows. Its effect on moist skin is to cause a cessation of the activity of sebaceous and sweat glands. That on ovarian function is to cause cessation of the activity of persistent and vulnerable follicles, and if the treatment is not too heavy, to allow normal follicles to recommence to function. That on inflammatory tissue is to cause death of lymphocytes and a rapid softening and death of tissue cells. It is improbable that there is a direct inhibiting or killing effect on bacteria. In other words, radium and x-rays are destructive agents, and this action is used in treating gynecologic lesions.

Radium is used in two forms—the active radium salt and radon, the emanation; both, so far as gynecology is concerned, exert the same effect. Radium is the more stable, expensive and unwieldy of the two. Radon is so unstable that losses in potency must be accounted for hourly or daily; however, it is less expensive than the active salt and can be put up in many different forms, strengths and sizes. Both are employed in various types and shapes of applicators with varied densities in their walls, either to allow the use of caustic beta rays or to screen them out and permit the use of only the very short, penetrating waves of gamma radiation. So far as gynecology

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is concerned, nearly all treatment is given in heavily screened applicators, in order to keep out the caustic beta rays whenever possible. Seeds, generally of 1 to 5 millicuries strength, are used for infiltrating nodules of tumor too small to permit the use of platinum needles. In most large areas, however, platinum needles are more and more taking the place of seeds; they vary in strength from 5 to 25 mg., and are of varying lengths and thicknesses. Radiation in cavities such as the cervical canal in cases of cancer is given by means of radium or radon in hollow tubes of brass, silver, gold or platinum. These applicators may contain tubes of any strength from 25 to 500 mg. or millicuries.

X-ray treatment is now in the throes of practical experimentation with higher voltages. The old 100-kv. machine is used only for superficial treatment. Even the 200-kv. machine, which was considered a high-voltage machine a few years ago, is now thought of as having too low a voltage. The 400-kv. or 500-kv. machine is considered to be adequate by some, but the 1000-kv. one[1] is now most talked of, and great results are expected from it. Enough time has not yet passed to allow proper evaluation of these higher voltages, and it remains to be seen whether the results with the 1000-kv. machine will surpass those obtained by the 200-kv. one. Human tissue can stand just so much radiation without undergoing necrosis, and if the amount of radiation needed to cause necrosis can be delivered into the depths without too great damage to the skin by the 200-kv. machine, the 1000-kv. apparatus may do no better, except that the skin will not be injured so much. Bladder symptoms,[2] bowel hemorrhages, intestinal obstruction, ureteral block and extensive pelvic fibrosis must be guarded against, and if any one of the machines mentioned can prevent such calamities and yet give a lethal dose to a deep, malignant growth, it should be the one of choice. A machine is now being made which will deliver 3000 kv. Great care and extensive study must be carried out before such an agent is used on human beings, and even then its employment should be confined to experts, and not be applied in routine therapy for a long time.

There is no doubt that the experience of the last few years with x-ray treatment in addition to radium has been highly significant in the treatment of cervical lesions.[3] After a long success with radium alone, the day of combined treatment has come. Its results are more satisfactory than the previous ones, and we may see a time when radium is entirely discarded. Radiation treatment is changing, and with more intelligent use of more powerful machines and even with new types of rays greater improvement may be expected.

Vulva. Pruritus vulvae, if of the moist type and due to oversecretion of the sebaceous and sweat glands, is well treated by light doses of x-rays. The dry type seen in patients with early senile changes does not respond well to radiation; estrogenic hormones given by mouth, intramuscular injection, or in salve or suppository form are more effective, but vulvectomy may be necessary.

Leukoplakic vulvitis, a precancerous lesion, due to overgrowth of the top layers of the skin with a marked lymphocytic infiltration beneath, is not well treated by radiation. Estrogenic hormones can be used for a short time, and if a result is not obtained quickly, complete removal of the vulva should be carried out.

Kraurosis vulvae, probably the end result of leukoplakic vulvitis, a dry lesion, is not suitable for radiation. The thin, parchment-like skin with its thick underlying connective tissue, characteristically accompanied by itching, is best let alone unless the severity of the symptoms makes necessary some form of treatment, when complete vulvectomy is the operation of choice.

Most radiologists and gynecologists have learned that the heavy doses of radium or x-ray necessary to destroy vulval cancer cause extreme discomfort and pain, and have given them up. The only proper treatment is complete vulvectomy with bilateral radical dissection of both groins after the method of Basset. Taussig[4, 5] has been America's greatest advocate of this operation, and his results surpass those of most other clinics. Vulval cancer is a disease of old women, but they are usually better surgical risks than they appear to be, and their life expectancy is longer with operation than it would be without; therefore radical surgery is justifiable. Some surgeons prefer to carry out a vulvectomy and to employ x-ray or interstitial radium treatment for the lymph nodes in the groins. This treatment is condemned, for the results are far less satisfactory than those following radical resection.

In certain cases recurrence of vulval cancer must be treated with radiation, and here it is best to use infiltration with gold seeds or platinum needles.

Clitoris. Carcinoma of the clitoris should be included under cancer of the vulva, and radical surgery — total vulvectomy and bilateral dissection of both groins — is to be preferred to any type of radiation.

Urethra. If excision of cancer of the urethra is possible, surgery is preferable to radiation. Sometimes it is not possible, and radium treatment is

instituted with the placing of platinum needles of proper length in the tumor, parallel to the urethra. The bladder is kept on constant drainage, and a massive dose of radium is given.

Cervix. Endocervicitis, once treated by moderate doses of radium in the cervical canal, is no longer so managed. Cancer of the cervix, whether squamous or adenomatous in type, whether early or advanced, is best treated by radium plus radiation by x-rays. Some gynecologists prefer radium alone, often applying x-ray treatment over the lower abdomen and back, possibly adding a vaginal cone.[6] Most gynecologists, however, prefer a combination of x-ray and radium; some give the radium first, and others the x-rays.

There is very little difference in the end results of any large series of cases, so long as they are adequately treated. In a recent report compiled by the San Francisco Gynecologic Society[7] on the basis of statistics from ten clinics in Europe and America, there was slight variation in the results except for one clinic, and there the method used was identical with that employed in one of the other clinics, the better results possibly being explained by the predominance of early cases. In nine of the clinics with quite different methods practically the same end results were obtained. There has been a fair increase in good results from the added roentgen-ray treatment. This is accounted for by the further injury done to cancer cells already partially destroyed by radium and by fibrosis of the pericervical tissue, and not to the destruction of metastatic lymph nodes. Enough surgery has been done following radiation to demonstrate that most cancerous lymph nodes in the pelvis are not destroyed by radiation.[5, 8] Unquestionably lymphatics are narrowed, cellular tissue is fibrosed, and cancer cells are injured, but destruction of cancer by radiation outside the field of the concentrated radium and x-ray treatment is not possible. However, fibrosis and destruction of lymph channels may easily prevent further extension of local disease. The work of Lynch,[9] showing cancer cells in the radiated cervix subsequently removed by a total hysterectomy, and that of Taussig,[5] who found cancerous nodes while doing pelvic dissections following radiation, offer proof that radiation does not destroy cancer outside certain areas.

The complications following treatment by radium or by radium and x-rays are not uncommon and may be disastrous. The vesicovaginal fistulas seen may be due to too-vigorous treatment or to advanced disease that has penetrated to the bladder floor. Cystoscopy before radiation will ordinarily indicate the latter, and sometimes if the disease is extensive small doses are best, for if the cancer is incurable, the patient's condition should not be made worse by too-powerful treatment. Rectovaginal fistulas are less common and are due to the same cause. For some reason they frequently heal spontaneously, but vesicovaginal fistulas practically never do so.

The necessity for careful investigation of the urinary tract[2] is obvious when the ureter is involved. Block of the ureter may be due either to the disease, to the disease together with swelling caused by radiation or to fibrosis following radiation. Every patient should be followed carefully by a urologist and given proper treatment, such as dilatation of the ureter or nephrostomy to prevent destruction of the kidney or ward off impending uremia.

Intestinal obstruction[10] is not uncommon following x-ray treatment, and occurs most often because of the continued treatment over a piece of bowel that is fixed at some point in the pelvis. The obstruction may be in the large or small bowel. It may be a fibrous, nodular block or a long, narrow stricture. An x-ray ileitis is set up, and later fibrosis occurs. This complication may follow the use of radium, especially in the too-active treatment of cancer of the cervical stump. Here a piece of intestine may be adherent to the stump and the close proximity of the radium applicator may cause a burn and later an area of fibrosis. Obstruction is a serious complication, and the presence of intestinal cramps following radiation suggests injury to the bowel.

Swelling of the leg following radiation treatment of cervical cancer is not always due to recurrent disease in the broad ligament, and one must be sure that cancer is present before advising radiation in the form of x-ray treatment. Such swelling is often due to pelvic fibrosis and lymphatic and venous block.

In many cases, radiation in the treatment of cervical cancer fails completely because of radiation insensitivity. Greater salvage will occur when this failure to respond is recognized earlier. The effect of combined x-ray and radium treatment can be noted by biopsy of the tissue under treatment, and a fair estimate of the ultimate result can be made.[11] If the response is not good a poor result can be expected, and vice versa. If this poor response is recognized and if the tumor can be removed by operation, serious consideration should be given to radical hysterectomy and dissection of the pelvic lymph nodes.

In most groups of early cases of cancer of the cervix treated by x-ray and radium, the salvage is about 60 per cent, so that 40 per cent of early cases must end in death in spite of the fact that they receive proper treatment. It is probable, therefore,

that as more careful studies are carried out to determine what patients in the operable group are not responding to radiation and should therefore be submitted to a radical surgical procedure, a better than 60 per cent salvage will be effected. Surgery has its place in cervical cancer. It is a modest place, and operative cases must be carefully selected, but if radiation resistance is recognized early more cures will result by subjecting the proper patients to operation.

Taussig[6] believes that x-rays will not kill the cancer cells in metastatic pelvic lymph nodes, and advocates dissection of the iliac, ureteral, hypogastric and obturator nodes in all early cases, especially those in which local vaginal disease can be destroyed with radiation. His end results from this operation are surprisingly good: of 11 patients with cancerous lymph nodes 3 are living and well without disease at the end of five years. The patients would surely have succumbed to the disease except for this ingenious operation. Surgery of the lymph nodes is better than radiation, and probably should be carried out.

Vagina. Cancer of the vagina, a very serious disease, should be treated like carcinoma of the cervix. External radiation through four portals should be given along with the intravaginal cone, in addition to radium needles in the center and the periphery of the tumor. The results will be poor. Fistulas, either in the bladder or rectum, will often occur. If the tumor lies in the outer vagina, dissection of the lymph nodes of the groin is essential if a good result is to be obtained. An operation of the Wertheim type can be undertaken in early cases, but it will never be so successful as radiation because of the great difficulty of removing the entire vagina. Even if it is removed, those tissues directly under the vaginal growth may be infiltrated by disease. Combined x-ray and radium treatment with the vaginal cone is the proper procedure.

Endometrium. Cancer of the endometrium is not primarily a lesion that should be treated by radiation. In some clinics radium is given to the exclusion of surgery, and the results as reported are fairly satisfactory. In most clinics the results by means of surgery are superior. Many gynecologists advise using intrauterine radium followed by x-ray treatment and then surgery, consisting of total hysterectomy — not of the radical type. Others advocate radiation in the uterine canal only, and then surgery. It has been very difficult to find an applicator that will destroy the cancer in the entire endometrial canal. Schmitz,[12] of Chicago, has devised such an apparatus. It is a Y-shaped piece of metal that contains needles in the two arms of the Y and in the shaft; after being placed in the canal the arms can be opened so as to fit into the cornua of the uterus. This method is unsatisfactory because of the separation of the needles in the various parts of the applicator. The Pondville Hospital has been using one long gold needle that fits snugly into a Monel metal applicator 1-mm. thick, and extends from its base to its top. The uterine cavity is measured accurately before the needle is made. Applicators vary from 5 to 15 cm. in length, so that any uterine cavity can be radiated throughout by means of an applicator of proper length. With this the tumor of the endometrium can be destroyed along its entire length, but areas of tumor that penetrate into the wall of the myometrium are not affected. At Pondville the reason for using radium in the uterine cavity is to prevent extension of this disease by metastasis to the anterior or posterior vaginal walls. The presence of such nodules practically always means a fatal outcome, and little can be done except local infiltration with radon seeds. To prevent such extension the whole uterine cavity is radiated and six weeks later the patient is operated on, in the hope that the tumor will be nearly destroyed, that the lymphatics will be closed off and that any tumor cells that may be spilled in the vaginal vault at operation will be gravely injured. X-ray treatment of lymph nodes involved by this disease is not satisfactory, because they are in the aortic and renal regions and not in the pelvis. The surgery that is undertaken after x-ray treatment should include the removal of the entire cervix and both tubes and ovaries, because these areas are susceptible to metastatic involvement. Often after radiation a sterile peritonitis is found, with fibrin and adhesions all through the pelvis. The most important part of the treatment of endometrial cancer is its surgical removal. Radiation has its use in attempts to prevent metastases, especially those to the vagina, or implantation into the vaginal scar.

Fallopian Tube. Carcinoma of the fallopian tube is rare; the treatment is radical pelvic surgery.[13] Radiation is only a secondary method of treatment, to be used after removal of the tubes, ovaries, uterus and cervix if an area of extension is found in the pelvis or if there are any evidences of pelvic metastases. The routine use of x-ray treatment is not essential.

Ovary. Cancer of the ovary is one of the most serious of all malignant lesions, and only about 9 per cent of patients with solid tumors survive for five years.[14] The papillary cystadenoma of the malignant type gives about a 21 per cent five-year

curability. Surgery is the proper treatment,[15] but if the tumor has become adherent, if there are areas that cannot be removed, or if there are metastatic nodules anywhere in the peritoneum, x-ray treatment should be resorted to. It should consist of rays directed against the metastases or extensions of tumor, the locations of which have been described to the roentgenologist as accurately as possible. Too many times the latter is called on to treat ovarian cancer without knowing where the radiation should be directed.

Certain types of endocrine tumors are extremely responsive to radiation, and if invasion has taken place anywhere in the peritoneal cavity, for instance, from a dysgerminoma of the ovary, this area should be treated immediately by x-ray, with some expectation of relief. Granulosal-cell tumors, supposedly radio-sensitive, may be radio-resistant, but x-ray treatment should be directed toward the metastases after they have been described to the roentgenologist.

There is no doubt that x-ray treatment prolongs life in inoperable cases of cancer of the ovary, but a cure is not effected. There are no authentic cases reported from the Massachusetts General Hospital of metastatic ovarian cancer that have been cured by x-ray treatment alone. It has made some of them operable, and following operation some of the patients have lived for a long time. By and large, x-ray treatment helps to prolong life and stop the accumulation of fluid. It is of extreme value for this reason, but radical surgery should never be avoided in the hope that x-ray treatment will furnish a proper substitute.

Benign Uterine Bleeding. In benign uterine bleeding in women near the menopause, radiation is extremely satisfactory. In any patient forty-five years of age or older who has abnormal bleeding proved by curettage to be benign, treatment by radium in the uterine cavity or by x-rays directed toward the ovaries is the one of choice. Every patient of this type who bleeds should be curetted to rule out cancer or submucous fibroids, and it is most satisfactory to place radium in the uterine cavity at that time. It is best given in the end of a long applicator that reaches the top of the fundus, so that there will be no scar in the cervix with subsequent pyometrium. Cases of bleeding after the menopause for which no reason can be found should never be treated by radium or x-ray, because of the possibility of obliterating the endometrial cavity, thus allowing the cause of the bleeding, such as a carcinoma or tumor of the ovary or tube, to be obscured. It is also possible to obliterate the cervical canal in such a way that the growth in the endometrial cavity will continue to enlarge for some time before being discovered.

In young girls it is rarely necessary to use radiation for menorrhagia; usually hormones, such as progesterone and testosterone, will check such bleeding until the patient's own cycle has been reestablished, which happens in most cases. Occasionally radium or x-ray in small doses can be used, but it is best not to treat this type of patient by radiation if it is possible to avoid it.

The effect of radium in benign bleeding cases is probably exerted on the ovary; it interferes with or destroys the follicles so that there are fewer or none left to secrete estrin. Not all the endometrium can be destroyed by a radium needle placed in the end of a long applicator in the uterine cavity, yet the bleeding does stop. Destruction of the activity of the ovary inactivates the endometrium; subsequently the latter atrophies, whereupon bleeding ceases. In about 95 per cent of cases with benign bleeding combined x-ray and radium treatment gives excellent results. There is no objection to x-ray treatment, but it is simpler, if a dilatation and curettage is to be done, to place radium at that time than to do the operation and then send the patient in for at least six x-ray treatments. It is purely a matter of convenience, not one of choice. Following radium treatment there is occasionally a moderate amount of vaginal discharge for two or three months. X-ray and radium are equally worth while, but radium is more convenient if it is available.

Fibroids. The treatment of fibroids with combined x-ray and radium should be confined to those patients who have a symmetrical, smooth tumor no larger than a grapefruit. Sending patients to the roentgenologist for treatment of fibroids by means of x-ray treatment without proper investigation of the uterine cavity and evaluation of the type of fibroid is to be condemned. Patients who have very large, rapidly growing, pedunculated or submucous fibroids, or who have a severe anemia or various other complications, should not be given x-ray treatment. The ideal tumor for radiation is one in the mid-line, smooth, without nodules, without any deviation of the uterine cavity, in a patient forty-five years of age or older but not past the menopause. There are not many fibroids that should be treated radiologically. Most should be treated surgically because of the many other pathologic lesions that are found in the pelvis at operation. Operation is to be preferred if the patient is under forty-five, because then the ovaries may be conserved, if possible, and an abrupt menopause avoided. Patients with bleeding who have passed the menopause should re-

ceive multiple curettages, and if bleeding does not cease, abdominal exploration and hysterectomy should be performed. Fibroids should never be treated with radiation after the menopause, because in most cases some other cause for the bleeding will be found, possibly an ovarian tumor, a carcinoma of the endometrium or some other serious lesion.

Endometriosis. Endometriosis is best treated by surgery. If the lesion is found to be extremely extensive and dissection of the rectum and sigmoid away from the back of the uterus practically impossible, or if there are multiple small intestinal adhesions in the pelvis, it may be well to avoid surgery. The diagnosis should be confirmed by means of biopsy, and x-ray treatment should be given to destroy the function of the ovary. The absence of the ovarian hormone will allow the endometrioma to shrink and atrophy. Radiation may be used in patients with recurrent endometriosis after a conservative operation has been performed.

Leiomyosarcoma. Leiomyosarcoma of the uterus is not satisfactorily treated with x-rays. True, there is evidence that this tumor is sensitive to radiation and will shrink under the influence of the rays, but a cure cannot be expected.

Miscellaneous. The use of x-ray treatment in patients with sterility, amenorrhea and abnormal bleeding has been discussed by Kaplan,[16] Mazer and Baer[17] and Rock et al.[18] In certain patients with amenorrhea due to a persistent follicle cyst that controls the endometrium, destruction of the cyst by moderate doses of x-rays allows other and younger follicles to develop, which after maturing cause menstrual periods to recur. This is a logical method of treating some patients with abnormal menstrual cycles.

X-ray treatment of the pituitary gland to affect the menstrual cycle in certain cases of dysfunction has not proved satisfactory, and should not be given until more positive evidence of successful results has been presented.

Summary

The present attitude toward x-ray and radium treatment of various gynecologic disorders is presented. Methods of radiation in pelvic disease are reaching their peaks, and it is probable that there will soon be an awakening of interest in surgical procedures as opposed to radiation.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 27021

PRESENTATION OF CASE*

A five-month-old female child entered the hospital because of jaundice.

The infant was born at home after an easy, normal delivery. No hemorrhages, skin lesions, or jaundice were noticed at the time of birth. When the child was three days old, slight jaundice was noticed, and at this same time the urine became deep yellow and the stools clay colored. The patient did not appear ill and, so far as is known, there was no fever. She nursed well at the breast. The jaundice persisted unchanged, as did the color characteristics of the stools and urine, until the age of three months. The informant stated that at this time "the whites of the eyes cleared, the stools became yellow, and the urine less dark." Throughout this period her appetite remained good and the weight gain adequate, so that at three months she weighed 10 pounds, 7 ounces, and was eating soft-solid foods. At four months of age, and associated with the eruption of teeth, the jaundice became severer, the stools white, and the urine dark brown. At this time painful urination was first noticed, in that the child cried before the act and ceased immediately afterward. Two weeks before entry the jaundice intensified, and the patient developed a fever of 101 to 102°F. The patient was studied in another hospital and then transferred.

The family history was noncontributory. The mother had had no stillbirths or miscarriages, and four siblings were alive and well. The mother's blood Wassermann test was allegedly negative, and there was no familial history of jaundice.

On examination the patient was a fairly well-developed and well-nourished, deeply jaundiced infant who was acutely and gravely ill. Breathing was rapid and shallow, with an expiratory grunt, but no limitation of chest motion was noted. The skin was deeply jaundiced, without petechiae, and there was good tissue turgor, with fair elasticity. There was a raised, reddish-blue hemangioma approximately 2.5 by 2 cm. in the epigastric region to the left of the midline. A single olive-sized, soft, discrete lymph node was present in the left axilla, with shotty cervical and inguinal nodes. The head was normal. The scleras and conjunctivas were markedly icteric. There was a profuse, thick, mucopurulent nasal discharge. The lips were dry and moderately pale; the mucous membranes were intact and icteric. The tonsils were reddened, and the posterior pharynx injected. The chest was fairly well developed, with a moderate amount of external beading, but no Harrison's groove. Examination of the lungs showed dullness to percussion at the right base posteriorly, with diminished breath sounds, a prolonged expiratory phase and many fine, crackling inspiratory rales over this area. The heart was enlarged to percussion; the rate was rapid, and the rhythm regular. There was a loud, blowing, systolic murmur heard all over the chest, both anteriorly and posteriorly, but loudest at the apex. The abdomen was greatly protuberant and distended, and the liver was palpable down to the iliac crest, its surface being smooth and firm, and its edge sharp. The spleen was also palpable down to the iliac crest and was slightly firm. The urethral meatus was slightly more posterior than normal, but the genitalia were otherwise normal. The tendon reflexes were hypoactive but equal; there were no meningeal signs.

The temperature was 101.2°F., the pulse 120, and the respirations 46.

Repeated examinations of the urine showed a specific gravity as high as 1.012 with a ++ test for albumin, a positive bile reaction and a persistent pyuria of moderate degree. On one occasion urine culture showed many colon bacilli. Examination of the blood showed a red-cell count of 2,490,000 with a hemoglobin of 52 per cent, and a white-cell count of 29,050 with 78 per cent polymorphonuclears, 19 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. The red cells were microcytic but hypochromic, with moderate polychromatophilia. Repeated blood examinations gave essentially the same results. The venous clotting time was 8 minutes, the nonprotein nitrogen of the blood serum 43 mg. per 100 cc., the serum proteins 6.4 gm., and the icteric index 150. The carbon dioxide combining power of the blood on one occasion was 40 vol. per cent and on another 75. A lumbar puncture yielded xanthochromic fluid under increased pressure with a + test for globulin, normal sugar, and a total protein of 46 mg. per 100 cc. The fluid contained 52 red cells and 14 white cells per cubic millimeter, 9 of which were polymorphonuclears. There was no growth on culture, and a titration Hinton test in dilutions up to 1:128 was negative.

*This case is presented through the courtesy of the Children's Hospital, Boston.

A throat culture on admission yielded many Type 17 pneumococci, and a blood culture grew hemolytic streptococci. Subsequent blood cultures were negative.

During hospitalization the patient ran a septic course, the temperature spiking to 105°F., and shortly after admission sulfathiazole therapy was instituted. The jaundice gradually intensified, and although the feces were usually clay colored, some were dark brown and appeared normal. By the end of the first hospital week the infant developed rather severe diarrhea, so that parenteral fluid therapy was necessary and three blood transfusions were given. The diarrhea increased to such an extent that everything was discontinued by mouth and a constant intravenous drip of aminoacid solution administered. On the fourteenth hospital day, because of microscopic hematuria, sulfathiazole was discontinued and sulfanilamide substituted. The patient died on the seventeenth hospital day. Terminally the nonprotein nitrogen of the blood rose to 68 mg. per 100 cc., and the icteric index to 300; a blood sodium was 158 milliequiv. per liter, and the blood chloride 110 milliequiv. Blood sulfanilamide determinations averaged 8 mg. per 100 cc., with a high of 22 mg. Urine sulfanilamide levels reached 104 mg. per 100 cc.

Differential Diagnosis

Dr. John D. Stewart: I might say at the outset that the most plausible diagnosis in this case is congenital malformation of the bile ducts. However, other possibilities have to be considered briefly.

Icterus neonatorum usually clears up by the end of the second week and is not associated with clay-colored stools or the presence of bile in the urine, and therefore may be dismissed from consideration. In the early history of this case erythroblastosis would have to be considered a definite possibility. However, the protracted five months' course, during which the jaundice was steadily maintained, would, according to my limited knowledge of erythroblastosis, exclude that diagnosis. The enlarged liver and spleen, of course, would go with erythroblastosis, but they would also be compatible with biliary cirrhosis based on prolonged obstruction of the bile flow. There was rather severe anemia, but despite repeated examinations of the blood there is no note that erythroblasts were found in the smear; the red cells were microcytic and hypochromic in type. Furthermore, a secondary anemia might well be found in obstructive jaundice of five months' duration with accompanying infection and malnutrition. The possibility that this might be jaundice on a hemolytic basis need not, in my opinion, be considered seriously. The duration was too long and the jaundice was more or less steady and of the obstructive type, with absence of bile in the stools most of the time and with bile in the urine.

Congenital syphilis has to be considered. It would have been a serious diagnostic possibility at the outset, until excluded by the allegedly negative maternal blood Wassermann test and by the negative Hinton test in the patient's cerebrospinal fluid. The hemangioma that is described at the left of the midline in the epigastrium and the olive-sized lymph node in the left axilla might make one pause for a moment, but I see no reason to suppose from the description of this lesion that it was malignant and might have metastasized and produced obstructive jaundice and enlargement of the liver. I mention it merely in passing. To me, by far the most plausible diagnosis is congenital malformation of the bile ducts. With obstructive jaundice it would certainly be unusual to have a spleen enlarged to the extent that this spleen was. However, I do not believe that should cast too much doubt on the diagnosis. Of course, enlargement of the liver is to be expected.

Interesting points in the clinical course are the fluctuation in the level of jaundice, and the fact that bile was at times excreted into the gastrointestinal tract. The extent of bilirubinemia in any given case depends on several factors. In the first place it depends on the degree of the obstruction to the excretion of bile; secondly, on the rate at which bilirubin is excreted through the kidneys; and, finally, on the rate at which bilirubin is formed. The rate of formation of bilirubin also depends on several factors, such as nutritional intake and whether or not blood transfusions are being given. In a patient with obstructive jaundice and complete blockage of the bile flow, the serum bilirubin level may rise after a blood transfusion. The question comes up as to whether any significant amounts of bile may be excreted through the intestinal mucosa. That has never been to me a very satisfactory theory. In the adult it is safe to say that in the presence of complete obstruction to the bile flow there will be no bile in the stools. This patient may, of course, have had only partial obstruction to the common duct, a stenosis rather than obliteration. If there is stenosis of the bile ducts without complete obliteration, varying degrees of infection and inspissation of the bile and mucus might produce temporary obstruction but not a sustained complete obstruction.

Patients with complete obliteration of the bile

ducts, as shown in a very excellent study made by Ayer,[1] die of two causes, namely, malnutrition and infection. Malnutrition undoubtedly was present in this case, although on the whole I am impressed with the meagerness of the evidence pointing to it. We have a statement that there was more or less normal weight gain at one point in the history, and the physical examination indicated no extensive disturbance of malnutrition at the time the patient entered the hospital. The type of malnutrition particularly to be expected in congenital obstruction to the biliary flow, and also in the adult patient with obstructive jaundice, is interference with the absorption of fat-soluble substances, because fatty substances are taken up in the intestine with the aid of bile salts. Hence vitamin A deficiency would be one of the things to be watched for and also a deficiency of vitamin K and impairment of the clotting mechanism. We have no evidence that there was any particular disturbance in the clotting power, and there is no direct evidence of vitamin A deficiency. However, it is possible that the pathologist at his examination found distinct evidence of vitamin A deficiency in the epithelium of the renal pelvis or in the respiratory mucosa. In connection with the matter of nutrition, it interests me that this patient was treated while in the hospital with parenteral aminoacid therapy, a fact which brings up the question of administering aminoacids or a high-protein diet to a patient with liver damage. There has been considerable dispute about it, but there seems to be a growing tendency to ignore the theoretical contraindications and treat patients with liver disease with a high dietary protein allowance.

This patient had sepsis for an indefinite time. There is direct evidence of infection in the urinary tract, and the child without doubt had pyelitis. The possibility that this pyelitis was based on a congenital anomaly of the urinary tract comes to mind. We have no way of deciding that question, but pyelitis in these patients is not uncommon in the absence of obstruction to urine flow. I therefore do not see that we have to postulate an anomaly of the urinary tract. There probably was a bronchopneumonia as a terminal complication. The question of whether there may have been infection in the liver also must be considered. In the reported cases this is unusual, and I see no reason to suspect that there was intrahepatic infection in this case.

It seems to me that there was not a great deal of evidence of interference with renal function. Protracted obstructive jaundice is often associated with impairment of renal function, but in the study that Ayer made of the renal tissue in the group of patients dying with congenital obstruction to the bile flow, significant lesions in the kidney, that is, lesions that might be associated with impaired function, were unusual. I am unable to interpret the cerebrospinal-fluid findings in this case. Whether they are related to kernicterus and changes in the brain I cannot say, but I think that is a good possibility. I see no reason to suppose there was meningitis. In conclusion I shall make a diagnosis of congenital malformation of the bile ducts with obstructive jaundice, biliary cirrhosis, pyelitis, a terminal pneumonia and bile nephrosis.

Dr. Harold L. Higgins: I should like to ask Dr. Stewart if he would have explored this child if the case had come to his attention before the final episode.

Dr. Stewart: In the material studied at the Children's Hospital, out of 45 cases with congenital obstruction to the flow of bile, 9 were found at operation to have lesions amenable to surgical treatment; therefore, there is a fair chance that surgical cure can be effected if the patient is in a condition warranting operation. There have been a number of patients who have grown to healthy maturity after operation for this condition.

Dr. Higgins: The terminal episode in this case fits in very well with vitamin A deficiency. Urinary obstruction might result from epithelial debris and lead to the pyelitis. Similar epithelial debris in the bronchi probably lead to the bronchopneumonia, which would have resulted fatally sooner if the patient had not been given sulfathiazole. Treatment with vitamin A parenterally would have been distinctly in order. I should expect that there were pathological findings of rickets; the mention of a rosary is made in the history.

Clinical Diagnoses

Obstructive jaundice (? congenital atresia of bile ducts).
Bronchopneumonia.

Dr. Stewart's Diagnoses

Congenital malformation of bile ducts, with obstructive jaundice.
Biliary cirrhosis.
Pyelitis.
Terminal pneumonia.
Bile nephrosis.

Anatomical Diagnoses

Bacteremia Type 17 pneumococcus and colon bacillus.
Bronchopneumonia, acute and chronic.

Pyelonephritis, mild, chronic (colon bacillus).
Atresia of extrahepatic biliary system, congenital, with agenesis of gall bladder and cystic duct.
Obstructive biliary cirrhosis.
Icterus, generalized, severe.
Annular pancreas.
Malformation of chordae tendineae to the aortic valve, congenital.
Coarctation of aorta just proximal to ductus arteriosus, moderate.

Pathological Discussion

Dr. Sidney Farber*: This is a complicated story, and I shall try to divide the findings into several groups. There was widespread infection in the lungs, both acute and chronic in type. That process had been going on for a number of weeks, with some organization of the exudate and a considerable amount of a fresh pneumonic process superimposed on the earlier one. Type 17 pneumococcus was found in the heart's blood at the time of autopsy, and the colon bacillus also. There was a pyelonephritis on the wane at the time of autopsy, so that I think we have every reason for assuming that both organisms had a perfect right to appear in the heart's blood. There was an otitis media with necrosis of the petrous portion of the temporal bone on one side, and a pneumococcus of the same type was cultured from that lesion. So much for the inflammatory changes. There was no evidence of meningitis — only edema and congestion of the brain.

Generalized icterus was present. The cause of this was found in an extensive malformation of the extrahepatic biliary system, which was responsible for obstructive biliary cirrhosis. The liver was considerably increased in size, very firm in consistence and deep green. The fibrosis secondary to the biliary obstruction was widespread enough to account for considerable portal obstruction. The spleen was four times the expected size for this age, and was the seat of considerable chronic passive congestion. There was a moderate degree of coarctation of the aorta just proximal to the ductus arteriosus. A second congenital vascular defect was a malformation of the chordae tendineae to the tricuspid valve, which caused a moderate degree of tricuspid insufficiency. A number of smaller and less important congenital abnormalities were found in various parts of the body.

The two most important abnormalities were the congenital malformation of the bile ducts and an unexpected malformation of the pancreas — an annular pancreas. Both were studied in great detail by Dr. Margaret Huntington, until recently a member of our laboratory staff. The common bile duct was represented by a fibrous cord extending from the junction of similar fibrous hepatic ducts to the ampulla of Vater. At the lower end of the common duct there was a cystlike expansion composed of fibrous tissue without a true lining of epithelial cells. A true lumen was present only in the terminal portion of this common duct, entering into the ampulla of Vater. The cystic duct was also represented by a delicate fibrous cord, which extended to the usual site of the gall bladder. There was no lumen in any portion of this duct or at the site of the gall bladder.

The body and tail of the pancreas were of normal form, but from the head there proceeded a narrow band of pancreatic tissue that encircled the first portion of the duodenum in ring fashion. This ring, which lay just above the ampulla of Vater, produced definite stenosis of the lumen of the duodenum. The main portion of the pancreas drained through the duct of Santorini to open into the first portion of the duodenum just above the pancreatic ring. Into this duct there emptied small channels, which drained the ring portion. A duct of Wirsung could not be found.

There was no histological evidence of vitamin A deficiency. There was, however, a very marked reduction in the amount of vitamin A in the liver, determined according to the method of May and McCreary,[2] so that we are forced to conclude that there was a deficiency of vitamin A at the time of death. There was evidence of slight rickets on histological examination. Some years ago Dr. Mark Altschule[3] studied a series of patients with congenital atresia of the bile ducts in our laboratory, and he found microscopic evidence of vitamin A deficiency in about 50 per cent.

I assume that an exploratory operation was not performed because of the pneumonic process. All patients with this general clinical picture are treated surgically, since surgical re-establishment of the extrahepatic biliary system, when possible, is the only effective treatment.

Dr. Stewart: Was there any kernicterus?

Dr. Farber: No; kernicterus is essentially a pathological and not a clinical diagnosis.

A Physician: Does a ring-shaped pancreas permit development to adult life?

Dr. Farber: Yes, about 50 cases are on record, and I think it has to be added to that very long list of causes of partial obstruction to the intestinal tract. Another case in an infant has turned up at the Children's Hospital since the one here described.

*Assistant professor of pathology, Harvard Medical School; pathologist, Children's Hospital, Boston.

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CASE 27022

Presentation of Case

A fifty-eight-year-old man entered the hospital complaining of precordial pain of six and a half hours' duration.

For an unstated period the patient had had slight substernal discomfort on climbing hills. At seven o'clock on the morning of admission he was seized with a severe precordial pain accompanied by a choking sensation. He described the pain as ascending diffusely from the pit of his stomach to his neck and shoulders. It abated somewhat, but four hours later returned in all its severity and radiated down both arms. The patient summoned his physician, who sent him immediately to the hospital.

The patient had had pneumonia eight years previously. The family history was irrelevant.

On examination the patient was well developed and well nourished, restless, and appeared acutely ill. He complained of substernal pain, arm discomfort and nausea. His color was ashen, with cyanosis of the lips and nailbeds. The scleras were clear; the pupils were equal and reacted to light and distance. Examination of the lungs was negative. The heart was enlarged to percussion, and on auscultation the sounds were distant and of poor quality, with a gallop rhythm at the apex. Systolic and diastolic murmurs were heard, loud at the base, faint at the apex. The aortic second sound was greater than the pulmonic. The pulses were equal and synchronous, but of poor quality and tension; the blood pressure was 200 systolic, 96 diastolic, in both arms. Examination of the abdomen was negative. Examination of the nervous system was negative.

The temperature was 98.6°F., the pulse 72, and the respirations 16.

An electrocardiographic recording showed normal rhythm with a rate of 60. There was left bundle-branch block, inverted T_1, diphasic T_2 and T_4, and a normal PR interval.

That evening, eleven hours after the first attack of substernal pain, the patient suddenly died.

Differential Diagnosis

Dr. Robert E. Glendy: It is apparent at first glance that we must decide whether this man had acute coronary thrombosis or whether he had something else. There seems to be little doubt that he did have angina pectoris on effort for an indefinite period before the onset of his acute illness. The description of the initial symptoms of the final episode might, if not subjected to too much scrutiny, be accepted as fairly typical of coronary thrombosis. It is not quite clear from the wording whether the onset of the pain was gradual, with progressive increase in severity, as one might expect with coronary thrombosis, or whether it was very sudden, reaching its maximum intensity quickly, as might be the case in dissecting aneurysm of the aorta. At first the pain radiated only to the neck and shoulder, then abated, and later radiated to the arms. This sequence of events does not seem to be of any particular significance in making a diagnosis of coronary thrombosis, whereas it is possible that if he had dissecting aneurysm the initial pain marked the intimal rupture and dissection within the coats of aorta, and the subsequent spread to the arms occurred when the proximal dissection involved one or both of the coronary orifices. The reason I raise this point is that it is rather unusual in dissecting aneurysm to have radiation of pain into the arms except, perhaps, when the coronary circulation has been involved by proximal dissection.

The past history affords no relevant information. Physical examination showed an acutely ill, ashen man with cyanosis of the lips and nailbeds. The degree of collapse described may occur in various cardiovascular emergencies. A blood pressure of 200 systolic, 96 diastolic certainly does not rule out coronary thrombosis, but it is quite against it. Were there any other blood-pressure determinations?

Dr. Tracy B. Mallory: That is all we have.

Dr. Glendy: The high blood pressure suggests the possibility of dissecting aneurysm of the aorta, because in this condition the pressure may be very high, even with an extreme degree of collapse. The negative findings in the lungs are significant, and I think they favor the diagnosis of dissecting aneurysm rather than any serious acute myocardial damage. Both the normal respiratory rate in the absence of dyspnea and orthopnea and the fact that the pulmonic second sound was not abnormal seem to bear this out. The enlargement of the heart certainly affords no etiologic clue, except that perhaps heart disease was present. The distant heart sounds, which were of poor quality, and the gallop rhythm likewise do not offer any important differential features. Incidentally, the term "gallop rhythm" is usually reserved for pulse rates above the normal range, but it is possible, I suppose, for the same mechanism to be in operation

at the slower rates of 72 and 60 when the heart is under considerable strain.

The muffled heart sounds I do not know exactly how to interpret. They may be due to weakening of the myocardium or possibly to an accumulation of fluid, which would undoubtedly, in this case, be blood in the pericardial sac.

The systolic and diastolic murmurs, maximal at the base of the heart, are, I believe, of considerable importance in arriving at a diagnosis. We have no previous history of rheumatic infection or syphilis, and nothing except the murmurs to suggest either of these conditions at this examination. The aortic second sound was described as present and greater than the pulmonic second sound. This certainly seems to be against any marked organic deformity or rigidity of the aortic valve that might be present with rheumatic or syphilitic heart disease.

What else might be responsible for such murmurs? Calcareous aortic-valve disease, possibly; but I think this is unlikely for the same reasons that I have just stated for rheumatic and syphilitic heart disease. The murmurs may have been pericardial in origin if there was fluid accumulating in the pericardial sac. Finally, the murmurs may have been, and I believe were, due to changes occurring in the aortic ring from dissecting aneurysm. We have no previous examination on which to base this conclusion, but such murmurs do appear fairly often in acute dissecting aneurysm owing to altered conditions in the aortic ring, and the mechanism is said to be due to the same factors that produce the murmurs in arteriovenous aneurysm, that is, the usual lumen of the aorta representing one vessel and the dissected portion the other, connected by a slit or rent in the intima.

The examinations of the abdomen and nervous system are reported as negative. There is no mention made of the peripheral pulses in the legs and feet. Do you know whether any observations were made?

DR. MALLORY: None were recorded.

DR. GLENDY: I am not surprised, because several years ago in reviewing 20 cases of dissecting aneurysm the clinical information, particularly in regard to peripheral pulsations, was very meager. I think that was largely due to the fact that when such a patient came in he was so ill that the doctors did not examine him completely, postponing it until a later time, which never came because the patient died. These people do not linger long.

The electrocardiogram showed left bundle-branch block, indicating coronary disease, but the disturbances in the T waves might occur with block alone, and I do not believe that there is anything in the tracing to indicate an acute myocardial process; this, again, would be against coronary thrombosis. I believe that this man had hypertensive coronary heart disease with cardiac enlargement, angina pectoris, and an acute dissecting aortic aneurysm, with at least proximal dissection and possibly distal dissection, the former involving the mouths of the coronary vessels; his sudden death was probably the result of rupture of this aneurysm into the pericardial sac or the mediastinum.

DR. MALLORY: Are there any alternative suggestions? Dr. Glendy has made his case very convincing.

DR. MILTON H. CLIFFORD: I can add nothing to the history. Very little could be found out about the past. The patient had seen a physician about six years before admission, but unfortunately no record of the blood pressure was made. The patient had always felt very well. When first seen he was not in any particularly acute shock, although a bit ashen. The blood pressure at that time was 170 systolic, 80 diastolic. It is evident that the shock must have increased greatly by the time he reached the hospital.

DR. PAUL D. WHITE: Dr. Mallory has handed me the electrocardiograms, and as Dr. Glendy stated, there is no evidence of any massive myocardial involvement, simply that of coronary heart disease, a clear-cut, well-marked left bundle-branch block, with T waves and ST segments in keeping with chronic coronary disease. There may be a normal-appearing electrocardiogram in the three clinical leads in the first few hours or days of coronary thrombosis, although there usually is an early change. If there had been massive enough myocardial involvement to kill the patient so quickly, one would expect more change.

DR. WILLIAM B. BREED: Is there anything in the electrocardiogram to suggest massive pulmonary infarction?

DR. WHITE: With bundle-branch block it may be impossible to detect complications. One cannot tell so much about what is going on as in normal complexes because the QRS and T waves in bundle-branch block are already greatly deformed. I cannot answer with certainty, but I should expect some change in the T waves, even in the presence of bundle-branch block, if massive pulmonary infarction were present. We have not, however, happened to encounter such a combination.

DR. BREED: With the story of pain in the chest, in spite of the negative chest examination at entrance, one must bring up the question of pulmonary embolism although I do not believe one can be definite. It should be considered.

DR. ROBERT S. PALMER: Rarely also one sees rup-

ture of the heart after coronary thrombosis. When would such rupture take place?

DR. WHITE: In going over a series of autopsies a few years ago we found that the average time of rupture of the heart after infarction was on the sixth day; of 16 cases, it occurred before the sixth day in 6, on the sixth day in 4, and after the sixth day in 6.

DR. EDWARD F. BLAND: We had 1 case in which it occurred in four or five days.

DR. WHITE: Have we seen any rupture within twenty-four hours, Dr. Mallory?

DR. MALLORY: I remember one that occurred in forty-eight hours. I think it has been reported within twenty-four.

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CLINICAL DIAGNOSES

Coronary occlusion.
Myocardial infarction.

DR. GLENDY'S DIAGNOSES

Hypertensive, coronary heart disease.
Cardiac hypertrophy.
Angina pectoris.
Dissecting aneurysm of the aorta, with proximal dissection involving the coronary orifices and rupture into the pericardium or mediastinum.

ANATOMICAL DIAGNOSES

Dissecting aneurysm of ascending aorta, with rupture.
Media necrosis cystica aortica.
Hemopericardium.
Cardiac hypertrophy.
Pheochromocytoma of the adrenal gland.
Nephrosclerosis.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The post-mortem examination confirms Dr. Glendy's predictions. There was a dissecting aneurysm of rather short extent. A horizontal tear was found in the intima of the aorta about 2 cm. above the aortic valve. There was dissection backward to the annulus fibrosus and the mouths of the coronary arteries, and forward as far as the arch of the aorta, where it stopped abruptly. There was no dissection of the abdominal or thoracic aorta. The aneurysm had ruptured externally into the pericardium, and since nearly 700 cc. of blood was present in the pericardial sac, it is reasonable to assume that the immediate mechanism of death was cardiac tamponade. The points of internal and external rupture were very near to each other.

DR. WHITE: Was the arch calcified?

DR. MALLORY: Yes; there was some calcification.

DR. WHITE: I wonder if the calcification stopped further dissection.

DR. MALLORY: It was limited to the intima, and since the plane of dissection was in the media, I should not think so.

DR. WHITE: I was thinking of the case that we saw last year with a rigid descending aorta, senile ectasia and a dissecting aneurysm of the ascending aorta; it was difficult or impossible for the dissection to continue down to the abdominal aorta.

DR. MALLORY: Occasionally in the abdominal aorta, calcification does extend deeply into the media and therefore might block dissection. In sections from most of this aorta there was no evidence of media necrosis cystica, but in the ascending aorta, the region of the dissection, there was clear evidence of it. I think that the dissection was limited to the portion of the aorta involved by the media necrosis cystica. There was considerable cardiac hypertrophy, — the heart weighed 550 gm., — which would suggest that the hypertension had been present for a significant period of time. The coronary arteries and the aortic valve were entirely normal.

One complete surprise of the autopsy was a tumor of the adrenal gland, centrally placed and small — about 1 cm. in diameter. This was a pheochromocytoma and may or may not have been responsible for the hypertension. There was also an ordinary nephrosclerosis.

DR. WHITE: You say that the coronary arteries were normal. I suppose there must have been some involvement of the smaller branches, unless this bundle-branch block could be attributed to an old infectious process, which would be much less likely.

DR. MALLORY: There was no gross involvement of the coronary arteries.

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THE MOST ANCIENT OF THE HEALING ARTS

AN Egyptian sculpture depicts King Akh-en-Aton and Queen Nefertiti (1375–1358 B.C.) holding out their children to be blessed by the healing hands of the Sun God. The king was one of the earliest Monotheists, and his god was the sun. Two thousand years before medicine could be called a science by any stretch of the imagination, physical therapy was being successfully employed by the Egyptians. In recent years there has been great change and advance in the methods and agents used in the treatment of many different diseases and lesions. The applicability and worth of physical therapy in many disorders seem to have been so forgotten by the regular school of medicine that its practice is becoming associated with certain cults. This situation is unfortunate for medicine and for its charges.

The prescription and administration of physical therapy are not the prerogatives of any specialty: they belong to general medicine. Physical therapy is as important in the treatment of cardiovascular diseases, disorders of the endocrine glands and chronic arthritic diseases as it is in neural disorders and orthopedic conditions. It is one of the most effective weapons of preventive medicine; it is the universal stimulator of convalescence. Thirty per cent of our countrymen drafted in World War I were rejected because of physical defects — and without doubt a still higher figure would hold true among women. The same percentage is anticipated, and, indeed, is being found, in the present conscription. Because the rehabilitating powers of physical therapy were demonstrated beyond cavil in the last war, it is safe to say that this disquieting number would be cut in halves if the medical profession could "sell" to American youth the simple prescriptions of preventive physical therapy.

What shall we do about the existing neglect of this most ancient art of healing? With his usual acuity Dr. Alan Gregg,* of the Rockefeller Foundation, has touched the sorest spot in the present situation: "A curious phenomenon in American medicine is the deft elimination of much reference to physical therapy, mindful, I suppose of the abuses imputed to osteopaths and chiropractors. . . .Thus protected our graduates angrily complain of competition from those whose knowledge it is tabu to acquire. The current unabashed ignorance of physical therapy in the country leaves it an excellent opportunity for development in American medicine." Dr. Gregg is correct — the fault lies in the medical schools. The first-rate schools are as guilty, if not guiltier, than the poor ones. With a few exceptions, hospital clinics of physical therapy are travesties on the name. Medical education is the heart of medicine, and physical therapy represents an essential artery of health. Can we not prevent it from becoming sclerotic?

*Gregg, A. Addenda to the agenda for the decade 1940-1950. *J. A. M. A.* 114:1139-1141, 1940.

There are a few voices crying in this wilderness of neglect. The Council on Physical Therapy of the American Medical Association is the loudest and most effective, but thus far the practical results have been meager except for hindering the sale of expensive and largely valueless apparatus to physicians in general practice. There is the "still small voice" of the Committee on Physical Therapy of the Massachusetts Medical Society, but physicians have turned an almost deaf ear to the five-year-old proddings of the committee and its offerings of postgraduate courses, exhibits and demonstrations. The medical schools, if they will, can convince their students of the importance of physical therapy and can provide the most efficient "hearing aid" for their graduates. This is one branch of medicine in the United States the rank and accomplishment of which compare most unfavorably with its dignity and effectiveness in other countries. "The sense of sin is the starting point of progress." It is high time we started.

It is a satisfaction to report that the Harvard Medical School, in co-operation with the Massachusetts General Hospital, has already taken steps to improve the teaching of physical therapy by the appointment of a medical physiotherapist as an assistant in medicine; he is also in charge of the newly equipped Department of Physical Therapy at the Massachusetts General Hospital.

THE MODERN DRUGSTORE

In a recent number of *Hygeia* appears an article that is heartening in indicating the increasing educational requirements and competence of professional pharmacists. The marketing of prescriptions to the laity is still a function of the so-called "drugstore," which, in reality, has become a department store. A survey of the prescription business, recently made, tabulates the returns received from 345 drugstores, distributed in such a way as to make an adequate sample of the country. In 1939, less than twelve per cent of the total revenue in these stores came from prescriptions. The average price for prescriptions was 91 cents each; the outlay for other items averaged 30 cents each. The former did not include the many purchases of medicines not made on prescription, and their high unit cost is probably one reason for the appalling amount of self-medication that goes on.

Presumably the cost of the prescription could be somewhat reduced by an increase in volume, since this is accompanied by an increase in prescription stock that is far less than that of the prescription sales. Furthermore, if one classifies the stores, either geographically or in relation to the size of the towns in which they are located, it appears that adequate profits are available to the drugstore regardless of these factors. It is apparent from the above-mentioned analysis that an increased use of prescriptions by doctors would make it possible to reduce their cost.

We, as doctors, are partly to blame for this situation. For a small temporary saving to the patient, we tell him "to buy a bottle of aspirin" or "to get some quinine." To be sure, it would cost the patient more if we wrote a prescription for these things until the practice was so general, and the volume of prescription business so large, that the pharmacist could afford to do away with the department-store end of his business. However, the basic difficulty lies with neither the pharmacist nor the doctor but primarily with the public. One pharmacist, who does a large prescription business, states that many of his regular clients demanded that he put in a lunch counter and soda fountain so that they would have something to do while waiting for their prescriptions to be filled. He finally succumbed, with great profit to himself.

The great problem of modern economics is that of distribution. We have attacked quality, advertising and production fairly successfully, but the problem of distribution remains to be solved in pharmacy as in many other spheres of merchandising.

MEDICAL EPONYM

Fowler's Solution

Fowler's Solution owes its name to Thomas Fowler (1736–1801), who in 1786 published an essay entitled "Medical reports of the effects of arsenic in the cure of agues, remitting fevers and periodic headachs." This was printed by J. John-

son, of London, in 1786. In his preface, the author, after calling attention to the fact that a patent medicine — Tasteless Ague and Fever Drops — had acquired some reputation in the country and had been found efficacious, says:

> In the Beginning of October, 1783, Mr. Hughes, the Apothecary to the Infirmary, (whose Industry, Attention and Abilities in his professional Line, justly merit Applause) informed the Author, that he had tried to imitate the Ague Drops, and, from a number of Experiments, had so far succeeded (his Medicine having produced similar Effects) that he was convinced they were a Preparation of Arsenic.
>
> In Consequence of this general Intimation, the Author of these Sheets consulted Lewis's Materia Medica upon Arsenic, and agreeable to his pharmaceutic History of that Article, he dissolved a small Portion of the white Sort in a Solution of the fixed vegetable Alkali. On trying and comparing the Effects of this Solution, with those of the Patent Ague Drops, he found the Medicine to be similar, but that the former was too Strong: he therefore diluted the Solution, by doubling the Proportion of Water, and then comparing their Effects, found the Medicines nearly of an equal Strength.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

COARCTATION OF THE AORTA IN PREGNANCY

Mrs. M. T., a thirty-two-year-old primipara, was seen on August 9, 1932, in the first month of pregnancy.

The family history was unimportant. The patient gave a history of scarlet fever, measles, pneumonia and mumps in childhood. She had had no serious illness after fifteen years of age. Four or five years before examination she had a period of excessive fatigue, when she was put to bed to rest for a week or two. At this time the systolic blood pressure was found to be 180, but it had not been taken since. Catamenia began at fourteen, were regular with a twenty-eight-day cycle and lasted about four days. The last period began on June 28, making the expected date of confinement April 4, 1933.

At the time of the first examination the patient had no symptoms. General physical examination was negative except for a systolic blood pressure of 170 and a loud blowing systolic murmur, loudest at the base. The urine was normal. The patient was referred at once to a cardiologist, whose opinion was as follows:

> The blood pressure is 180 systolic, 100 diastolic, in the arms; the arteries in the legs are barely palpable, and the pulsations so faint that I cannot take the pressure by ordinary measures. The heart has a very loud systolic murmur, loudest at the base, where it is transmitted upward; it can be heard very clearly down the back. These findings are associable with a congenital malformation in the aorta somewhere below the point where the left subclavian comes off. The abbreviated diagnosis is coarctation of the aorta, but I think the trouble is further down the aorta than this diagnosis strictly suggests. The x-ray examination is somewhat unsatisfactory because the patient is so young that the arteries do not show clearly. Nevertheless, the films show a change in the outline of the descending aorta. There is no evidence of nephritis or other disease.
>
> Of course, no one knows what influence this condition may have on pregnancy. There is justification, however, in treating the case as one would a Class I cardiac patient. I have therefore prescribed the usual regime, and asked her to report at regular intervals.
>
> The only thing that enters my mind is the possibility that the pregnancy may be interfered with because of the abnormally low blood supply to the lower part of the body, which might interfere with the development of the fetus. Pregnancy is supposed to be rare among patients with coarctation of the aorta because their bodies are ill nourished below the point of narrowing and their internal genitalia may be poorly developed. But this patient, unlike many of those with coarctation of the aorta, seems to be symmetrically developed.

From this time on the patient was kept under close observation by both the obstetrician and the cardiologist, and her activities were restricted exactly as if she had been a Class I cardiac patient. The pregnancy progressed uneventfully until December 30, when she reported that she had not felt any fetal motion for a week. The uterus was the size of a six and a half months' pregnancy, there appeared to be an excess of fluid, and no fetal heart could be heard. X-ray examination showed a moderate hydramnios and a probably dead fetus. From this time on the uterus did not enlarge, and on March 9 the patient went into labor and delivered a stillborn, macerated fetus. There was no obvious cause for the intrauterine fetal death. The blood pressure had been persistently elevated throughout the pregnancy, at times being 200 systolic. The puerperium was uncomplicated.

Ten months later the patient became pregnant for the second time. She was again kept under close observation by the cardiologist and treated as a patient with organic heart disease. The pregnancy was entirely uneventful; the patient went into spontaneous labor at term and was delivered normally of a baby boy weighing 9 pounds,

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

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11 ounces. The convalescence was uncomplicated.

About two and a half years later the patient became pregnant for the third time, and again went through her pregnancy without complications and was delivered normally at term of a baby girl weighing 7 pounds, 3 ounces.

At the present time, four years later, this patient is forty years old, is in the eighth month of her fourth pregnancy, has a systolic blood pressure of 170 or 180 but is otherwise entirely well. She has been kept on the same cardiac regime as in the other pregnancies, and a normal termination of the pregnancy is expected.

Comment. This case is reported because of its rarity and to show that coarctation of the aorta in no way contraindicates pregnancy or pelvic delivery.

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MEDICAL-COSTS INSURANCE

To The Editor: The following correspondence will undoubtedly be of interest to the members of the Massachusetts Medical Society.

WALTER G. PHIPPEN, M.D.

* * *

Dear Dr. Phippen:

Following the publication in the *New England Journal of Medicine* of the votes of the Council of the Massachusetts Medical Society in regard to the development of a prepayment insurance plan to cover the costs of medical care, individual members of the Society and the lay press reached the erroneous conclusion that the Society was endeavoring to develop control over all medical-service plans.

Since then the lay press has frequently asked the White Cross and Medical and Surgical Associates if there was a conflict between the Massachusetts Medical Society and the White Cross. Both the organizations asked have taken pains to make it clear to the press that although the preliminary synopsis approved by the Council might be given a monopolistic interpretation and suggest a conflict, they were sure that any ambiguity which appeared in the preliminary synopsis would be eliminated in the final draft.

Despite this, articles have appeared several times in the lay press suggesting that there would be a conflict between the Massachusetts Medical Society and other groups that offer medical service on a prepayment basis. The most recent one noted by us appeared in the *Quincy Tribune*. All such articles seem to us to be very unfortunate, and we fear that they may interfere with the development of constructive plans for the delivery of medical service on a prepayment basis.

We can assure you that neither the White Cross nor Medical and Surgical Associates has instigated or authorized anyone connected with the management of either to prepare such an article. Furthermore, we believe that several plans should be developed for the delivery of medical care on a prepayment basis, so that by trial and error the best plan or plans for the public welfare may be secured.

We fear that suspicion still exists in some quarters that the Massachusetts Medical Society is endeavoring to create a monopoly, and we respectfully suggest that you make an announcement in the *Journal* similar to the one which you have made to one of us personally, namely, that the Society has no idea of trying to establish a monopoly.

As a step toward clarifying the situation and eliminating unfounded suspicions we shall be glad to have you publish this letter in the *New England Journal of Medicine.*

Sincerely yours,

Channing Frothingham, *Chairman,*
MEDICAL AND SURGICAL ASSOCIATES.

73 Tremont Street,
Boston.

Dear Dr. Frothingham:

Your letter of recent date is at hand. Inasmuch as several members of the Society have written me in regard to the appearance of articles in the lay press concerning prepayment plans for medical care, I am very glad to publish your letter disclaiming responsibility for these unfortunate publications.

May I take this opportunity to say what has been said before, namely, that the draft of the enabling act presented by Dr. Lanman's committee was merely a preliminary draft. You may remember that I asked that no action be taken by the Council but that the committee desired constructive criticism. The criticisms so received have been duly considered by the committee and will be presented at the next meeting of the Council in February.

So far as we have been able to determine from legal counsel of the Massachusetts Medical Society, our bill does not interfere with any existing plan. The Massachusetts Medical Society believes that any plan that it sponsors should comply with the laws governing insurance in Massachusetts and that it have supervisory control through properly appointed general and local committees of any plan so established. I am sure it does not contemplate a monopoly.

Very sincerely,

Walter G. Phippen, *President,*
MASSACHUSETTS MEDICAL SOCIETY.

31 Chestnut Street,
Salem, Massachusetts.

MEDICAL POSTGRADUATE EXTENSION COURSES

The following sessions, given by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health, the United States Public Health Service and the Federal Children's Bureau, have been arranged for the week beginning January 12:

MIDDLESEX EAST

Tuesday, January 14, at 4:15 p.m., at the Melrose Hospital, Melrose. The Clinical Recognition of the Types of Jaundice and Recent Advances in Their Treatment. Instructor: Franz Ingelfinger. Walter H. Flanders, *Chairman.*

MIDDLESEX SOUTH

Tuesday, January 14, at 4:00 p.m., at the Cambridge Hospital, Mt. Auburn Street, Cambridge. Pediatric Case Discussions. Instructor: Warren R. Sisson. Dudley Merrill, *Chairman.*

NORFOLK

Thursday, January 16, at 8:30 p.m., at the Norwood Hospital, Norwood. Dermatitis and Eczema. Instructor: Bernard Appel. Hugo B. C. Riemer, *Chairman*.

NORFOLK SOUTH

Monday, January 13, at 8:30 p.m., at the Quincy City Hospital, Quincy. Diagnosis and Treatment of Minor Lesions of Rectum and Anus. Instructor: Franklin G. Balch, Jr. David L. Belding, *Chairman*.

SUFFOLK

Thursday, January 16, at 4:30 p.m., in John Ware Hall, Boston Medical Library. Therapeutic Uses of Preparations of Endocrine Glands: Thyroid gland, pituitary gland, ovary, testis and adrenal cortex. Instructor: William T. Salter. Reginald Fitz, *Chairman*.

DEATHS

CRAWFORD — Joseph W. Crawford, M.D., of North Adams, died November 7. He was in his sixty-ninth year.

Dr. Crawford received his degree from the Hahnemann Medical College and Hospital of Philadelphia in 1900. He was a fellow of the Massachusetts Medical Society and the American Medical Association, and also held membership in the Radiological Society of North America. He was on the staff of the North Adams Hospital.

CURRAN — Charles H. Curran, M.D., of Springfield, died September 10. He was in his fifty-first year.

Dr. Curran received his degree from the University of the City of New York Medical Department in 1886. He was a former member of the Massachusetts Medical Society.

FITZPATRICK — Francis J. Fitzpatrick, M.D., of Somerville, died January 2. He was in his sixtieth year.

Born in Charlestown, he attended Boston College and received his degree from the College of Physicians and Surgeons in Boston in 1928. Dr. Fitzpatrick was a member of the Somerville Board of Public Welfare at the time of his death. He was a member of the Massachusetts Medical Society and the American Medical Association.

PAGE — Joseph G. E. Page, M.D., of Southbridge, died December 28. He was in his seventieth year.

Born in Soral, Quebec, he attended St. Hyacinthe College and Laval University, Quebec, and received his degree from the University of Montreal Faculty of Medicine in 1895. He served as a member of the Southbridge Board of Health for a number of years and was formerly associate medical examiner of that district. Dr. Page was a member of the Massachusetts Medical Society and of the American Medical Association.

His widow, a son, a daughter and a grandchild survive him.

MISCELLANY

GREATER BOSTON COMMUNITY FUND

Dr. Earle M. Chapman will head the Physicians' Group of the Professional Division of Industry and Finance in the Greater Boston Community Fund's 1941 Campaign to raise $4,883,000 between January 18 and February 5.

The ten committees, each under the direction of a vice-chairman, are composed as follows:

P. C. Baird, vice-chairman. Committeemen: A. G. Brailey, R. W. Daffinee, R. E. Fleming, Ashton Graybiel, E. P. Hayden, W. F. Lever, W. J. Macdonald, Sylvester McGinn, A. S. Rose, Charles Short, O. S. Staples, S. H. Sturgis.

J. M. Baty, vice-chairman. Committeemen: R. C. Eley, M. N. Fulton, Harold Freedman, Theodore Bennett.

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W. I. Gregg, vice-chairman. Committeemen: Herbert Adams, J. S. Mansfield, R. B. Miller, H. I. Suby, Richard Warren.

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Maurice Strauss, vice-chairman. Committeemen: F. G. Balch, Jr., J. M. Faulkner, T. H. Ham, J. C. Harberson, W. P. Murphy, W. R. Ohler, G. C. Prather, H. H. Rosenfield, C. P. Sheldon.

The Hospital Group of the Institutions' Division of Industry and Finance is headed by Dr. Norbert A. Wilhelm, superintendent of the Peter Bent Brigham Hospital. He will be assisted by over a hundred physicians who are members of the hospital staffs of Greater Boston.

CORRESPONDENCE

STATE MENTAL HOSPITALS, LISTED ACCORDING TO CITIES AND TOWNS

To the Editor: Following is a list of the cities and towns within the Commonwealth; opposite the name of each is indicated the mental hospital to which patients suffering from psychosis should be referred whenever hospitalization becomes necessary. The list is derived from a revision of hospital districts within the State which became effective October 1, 1940, and was necessitated chiefly by the fact that certain hospitals were receiving a greater number of admissions than could be properly accommodated.

Committing courts were advised of the change at the time. It now appears, however, that the information has not reached many physicians in the Commonwealth.

Clifton T. Perkins, *Commissioner, Department of Mental Health.*

100 Nashua Street, Boston.

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CITY OR TOWN	COUNTY	STATE MENTAL HOSPITAL
Abington	Plymouth	Taunton
Acton	Middlesex	Worcester
Acushnet	Bristol	Taunton
Adams	Berkshire	Northampton
Agawam	Hampden	Northampton
Alford	Berkshire	Northampton
Amesbury	Essex	Danvers
Amherst	Hampshire	Northampton
Andover	Essex	Danvers
Arlington	Middlesex	Westborough
Ashburnham	Worcester	Gardner
Ashby	Middlesex	Gardner
Ashfield	Franklin	Northampton
Ashland	Middlesex	Westborough
Athol	Worcester	Gardner
ATTLEBORO	Bristol	Foxborough and Taunton
Auburn	Worcester	Worcester
Avon	Norfolk	Foxborough
Ayer	Middlesex	Gardner
Barnstable	Barnstable	Taunton
Barre	Worcester	Worcester
Becket	Berkshire	Northampton
Bedford	Middlesex	Worcester
Belchertown	Hampshire	Northampton
Bellingham	Norfolk	Foxborough
Belmont	Middlesex	Westborough
Berkley	Bristol	Taunton
Berlin	Worcester	Worcester
Bernardston	Franklin	Northampton
BEVERLY	Essex	Danvers
Billerica	Middlesex	Worcester
Blackstone	Worcester	Grafton
Blandford	Hampden	Northampton
Bolton	Worcester	Worcester
BOSTON	Suffolk	
Bourne	Barnstable	Taunton
Boxborough	Middlesex	Gardner
Boxford	Essex	Danvers
Boylston	Worcester	Worcester
Braintree	Norfolk	Medfield
Brewster	Barnstable	Taunton
Bridgewater	Plymouth	Foxborough and Taunton
Brimfield	Hampden	Worcester
BROCKTON	Plymouth	Foxborough and Taunton
Brookfield	Worcester	Worcester
Brookline	Norfolk	Worcester
Buckland	Franklin	Northampton
Burlington	Middlesex	Worcester
Cambridge	Middlesex	Westborough
Canton	Norfolk	Foxborough
Carlisle	Middlesex	Worcester
Carver	Plymouth	Taunton
Charlemont	Franklin	Northampton
Charlton	Worcester	Grafton
Chatham	Barnstable	Taunton
Chelmsford	Middlesex	Worcester
CHELSEA	Suffolk	Danvers
Cheshire	Berkshire	Northampton
Chester	Hampden	Northampton
Chesterfield	Hampshire	Northampton
CHICOPEE	Hampden	Northampton
Chilmark	Dukes	Taunton
Clarksburg	Berkshire	Northampton
Clinton	Worcester	Worcester
Cohasset	Norfolk	Medfield
Colrain	Franklin	Northampton
Concord	Middlesex	Worcester
Conway	Franklin	Northampton
Cummington	Hampshire	Northampton
Dalton	Berkshire	Northampton
Dana	Worcester	Gardner
Danvers	Essex	Danvers
Dartmouth	Bristol	Taunton
Dedham	Norfolk	Medfield
Deerfield	Franklin	Northampton
Dennis	Barnstable	Taunton
Dighton	Bristol	Taunton
Douglas	Worcester	Grafton
Dover	Norfolk	Medfield
Dracut	Middlesex	Worcester
Dudley	Worcester	Grafton
Dunstable	Middlesex	Worcester
Duxbury	Plymouth	Taunton
East Bridgewater	Plymouth	Foxborough and Taunton
East Brookfield	Worcester	Worcester
East Longmeadow	Hampden	Northampton
Eastham	Barnstable	Taunton
Easthampton	Hampshire	Northampton
Easton	Bristol	Taunton
Edgartown	Dukes	Taunton
Egremont	Berkshire	Northampton
Enfield	Hampshire	Worcester
Erving	Franklin	Gardner
Essex	Essex	Danvers
EVERETT	Middlesex	Worcester
Fairhaven	Bristol	Taunton
FALL RIVER	Bristol	Taunton
Falmouth	Barnstable	Taunton
FITCHBURG	Worcester	Gardner
Florida	Berkshire	Northampton
Foxborough	Norfolk	Foxborough
Framingham	Middlesex	Westborough
Franklin	Norfolk	Foxborough
Freetown	Bristol	Taunton
GARDNER	Worcester	Gardner
Gay Head	Dukes	Taunton
Georgetown	Essex	Danvers
Gill	Franklin	Northampton
GLOUCESTER	Essex	Danvers
Goshen	Hampshire	Northampton
Gosnold	Dukes	Taunton
Grafton	Worcester	Grafton
Granby	Hampshire	Northampton
Granville	Hampden	Northampton
Great Barrington	Berkshire	Northampton
Greenfield	Franklin	Northampton
Greenwich	Hampshire	Worcester
Groton	Middlesex	Gardner
Groveland	Essex	Danvers
Hadley	Hampshire	Northampton
Halifax	Plymouth	Foxborough and Taunton
Hamilton	Essex	Danvers
Hampden	Hampden	Northampton
Hancock	Berkshire	Northampton
Hanover	Plymouth	Taunton
Hanson	Plymouth	Taunton
Hardwick	Worcester	Worcester
Harvard	Worcester	Worcester
Harwich	Barnstable	Taunton
Hatfield	Hampshire	Northampton
HAVERHILL	Essex	Danvers
Hawley	Franklin	Northampton
Heath	Franklin	Northampton
Hingham	Plymouth	Taunton
Hinsdale	Berkshire	Northampton
Holbrook	Norfolk	Medfield
Holden	Worcester	Worcester
Holland	Hampden	Worcester
Holliston	Middlesex	Westborough
HOLYOKE	Hampden	Northampton
Hopedale	Worcester	Grafton
Hopkinton	Middlesex	Westborough
Hubbardston	Worcester	Gardner
Hudson	Middlesex	Westborough
Hull	Plymouth	Taunton
Huntington	Hampshire	Northampton
Ipswich	Essex	Danvers
Kingston	Plymouth	Taunton
Lakeville	Plymouth	Taunton
Lancaster	Worcester	Worcester
Lanesborough	Berkshire	Northampton
LAWRENCE	Essex	Danvers
Lee	Berkshire	Northampton
Leicester	Worcester	Worcester
Lenox	Berkshire	Northampton
LEOMINSTER	Worcester	Gardner
Leverett	Franklin	Northampton
Lexington	Middlesex	Worcester
Leyden	Franklin	Northampton
Lincoln	Middlesex	Worcester
Littleton	Middlesex	Gardner
Longmeadow	Hampden	Northampton
LOWELL	Middlesex	Worcester
Ludlow	Hampden	Northampton
Lunenburg	Worcester	Gardner
LYNN	Essex	Danvers
Lynnfield	Essex	Danvers
MALDEN	Middlesex	Worcester
Manchester	Essex	Danvers
Mansfield	Bristol	Foxborough and Taunton
Marblehead	Essex	Danvers
Marion	Plymouth	Taunton
MARLBOROUGH	Middlesex	Westborough
Marshfield	Plymouth	Taunton
Mashpee	Barnstable	Taunton
Mattapoisett	Plymouth	Taunton
Maynard	Middlesex	Worcester
Medfield	Norfolk	Medfield
MEDFORD	Middlesex	Worcester
Medway	Norfolk	Foxborough
MELROSE	Middlesex	Worcester
Mendon	Worcester	Grafton
Merrimac	Essex	Danvers
Methuen	Essex	Danvers
Middleborough	Plymouth	Taunton
Middlefield	Hampshire	Northampton
Middleton	Essex	Danvers
Milford	Worcester	Grafton
Millbury	Worcester	Worcester
Millis	Norfolk	Foxborough

Millville	Worcester	Grafton
Milton	Norfolk	Medfield
Monroe	Franklin	Northampton
Monson	Hampden	Worcester
Montague	Franklin	Northampton
Monterey	Berkshire	Northampton
Montgomery	Hampden	Northampton
Mount Washington	Berkshire	Northampton
Nahant	Essex	Danvers
Nantucket	Nantucket	Taunton
Natick	Middlesex	Westborough
Needham	Norfolk	Medfield
New Ashford	Berkshire	Northampton
NEW BEDFORD	Bristol	Taunton
New Braintree	Worcester	Worcester
New Marlborough	Berkshire	Northampton
New Salem	Franklin	Gardner
Newbury	Essex	Danvers
NEWBURYPORT	Essex	Danvers
NEWTON	Middlesex	Westborough
Norfolk	Norfolk	Foxborough
NORTH ADAMS	Berkshire	Northampton
North Andover	Essex	Danvers
North Attleboro	Bristol	Foxborough and Taunton
North Brookfield	Worcester	Worcester
North Reading	Middlesex	Worcester
NORTHAMPTON	Hampshire	Northampton
Northborough	Worcester	Westborough
Northbridge	Worcester	Grafton
Northfield	Franklin	Northampton
Norton	Bristol	Foxborough and Taunton
Norwell	Plymouth	Taunton
Norwood	Norfolk	Medfield
Oak Bluffs	Dukes	Taunton
Oakham	Worcester	Worcester
Orange	Franklin	Gardner
Orleans	Barnstable	Taunton
Otis	Berkshire	Northampton
Oxford	Worcester	Grafton
Palmer	Hampden	Worcester
Paxton	Worcester	Worcester
PEABODY	Essex	Danvers
Pelham	Hampshire	Northampton
Pembroke	Plymouth	Taunton
Pepperell	Middlesex	Gardner
Peru	Berkshire	Northampton
Petersham	Worcester	Gardner
Phillipston	Worcester	Gardner
PITTSFIELD	Berkshire	Northampton
Plainfield	Hampshire	Northampton
Plainville	Norfolk	Foxborough
Plymouth	Plymouth	Taunton
Plympton	Plymouth	Taunton
Prescott	Hampshire	Worcester
Princeton	Worcester	Worcester
Provincetown	Barnstable	Taunton
QUINCY	Norfolk	Medfield
Randolph	Norfolk	Medfield
Raynham	Bristol	Taunton
Reading	Middlesex	Worcester
Rehoboth	Bristol	Taunton
REVERE	Suffolk	Danvers
Richmond	Berkshire	Northampton
Rochester	Plymouth	Taunton
Rockland	Plymouth	Taunton
Rockport	Essex	Danvers
Rowe	Franklin	Northampton
Rowley	Essex	Danvers
Royalston	Worcester	Gardner
Russell	Hampden	Northampton
Rutland	Worcester	Worcester
SALEM	Essex	Danvers
Salisbury	Essex	Danvers
Sandisfield	Berkshire	Northampton
Sandwich	Barnstable	Taunton
Saugus	Essex	Danvers
Savoy	Berkshire	Northampton
Scituate	Plymouth	Taunton
Seekonk	Bristol	Taunton
Sharon	Norfolk	Foxborough
Sheffield	Berkshire	Northampton
Shelburne	Franklin	Northampton
Sherborn	Middlesex	Westborough
Shirley	Middlesex	Gardner
Shrewsbury	Worcester	Worcester
Shutesbury	Franklin	Northampton
Somerset	Bristol	Taunton
SOMERVILLE	Middlesex	Westborough
South Hadley	Hampshire	Northampton
Southampton	Hampshire	Northampton
Southborough	Worcester	Westborough
Southbridge	Worcester	Grafton
Southwick	Hampden	Northampton
Spencer	Worcester	Worcester
SPRINGFIELD	Hampden	Northampton
Sterling	Worcester	Worcester
Stockbridge	Berkshire	Northampton
Stoneham	Middlesex	Worcester
Stoughton	Norfolk	Foxborough
Stow	Middlesex	Worcester
Sturbridge	Worcester	Grafton
Sudbury	Middlesex	Westborough
Sunderland	Franklin	Northampton
Sutton	Worcester	Worcester
Swampscott	Essex	Danvers
Swansea	Bristol	Taunton
TAUNTON	Bristol	Taunton
Templeton	Worcester	Gardner
Tewksbury	Middlesex	Worcester
Tisbury	Dukes	Taunton
Tolland	Hampden	Northampton
Topsfield	Essex	Danvers
Townsend	Middlesex	Gardner
Truro	Barnstable	Taunton
Tyngsborough	Middlesex	Worcester
Tyringham	Berkshire	Northampton
Upton	Worcester	Grafton
Uxbridge	Worcester	Grafton
Wakefield	Middlesex	Worcester
Wales	Hampden	Worcester
Walpole	Norfolk	Foxborough
WALTHAM	Middlesex	Westborough
Ware	Hampshire	Worcester
Wareham	Plymouth	Taunton
Warren	Worcester	Worcester
Warwick	Franklin	Gardner
Washington	Berkshire	Northampton
Watertown	Middlesex	Westborough
Wayland	Middlesex	Westborough
Webster	Worcester	Grafton
Wellesley	Norfolk	Medfield
Wellfleet	Barnstable	Taunton
Wendell	Franklin	Gardner
Wenham	Essex	Danvers
West Boylston	Worcester	Worcester
West Bridgewater	Plymouth	Foxborough and Taunton
West Brookfield	Worcester	Worcester
West Newbury	Essex	Danvers
West Springfield	Hampden	Northampton
West Stockbridge	Berkshire	Northampton
West Tisbury	Dukes	Taunton
Westborough	Worcester	Westborough
WESTFIELD	Hampden	Northampton
Westford	Middlesex	Gardner
Westhampton	Hampshire	Northampton
Westminster	Worcester	Gardner
Weston	Middlesex	Westborough
Westport	Bristol	Taunton
Westwood	Norfolk	Medfield
Weymouth	Norfolk	Medfield
Whately	Franklin	Northampton
Whitman	Plymouth	Taunton
Wilbraham	Hampden	Worcester
Williamsburg	Hampshire	Northampton
Williamstown	Berkshire	Northampton
Wilmington	Middlesex	Worcester
Winchendon	Worcester	Gardner
Winchester	Middlesex	Worcester
Windsor	Berkshire	Northampton
Winthrop	Suffolk	Danvers
WOBURN	Middlesex	Worcester
WORCESTER	Worcester	Worcester
Worthington	Hampshire	Northampton
Wrentham	Norfolk	Foxborough
YARMOUTH	Barnstable	Taunton

RESTORATION OF LICENSE

To the Editor: The license of Dr. Anthony P. Carogana, 672 Broadway, Chelsea, Massachusetts, which was revoked on July 11, 1940, was restored by the Board of Registration in Medicine on December 19, 1940.

STEPHEN RUSHMORE, M.D., *Secretary,*
Board of Registration in Medicine.

State House,
Boston.

NOTICES

WILLIAM HARVEY SOCIETY

There will be a lecture on "Relation of the Internal Secretions to Cancer" by Dr. Joseph C. Aub, sponsored by the William Harvey Society of the Tufts College Medical School, on Friday, January 17, at 8 p.m., in the auditorium

of the Beth Israel Hospital. Dr. S. J. Thannhauser will be chairman of the meeting.

All interested members of the medical profession are cordially invited.

BOSTON SOCIETY OF BIOLOGISTS

There will be a meeting of the Boston Society of Biologists in the Ether Dome of the Massachusetts General Hospital on Wednesday, January 22, at 8 p.m. Dinner will be served in the dining room of the hospital at 7 p.m.

PROGRAM

Vitamin A Absorption Curves. Drs. John McCreary and Charles May.

Vitamin A and Night-Blindness: A laboratory and field study. Dr. George Wald.

Disproportionate Growth of Skeleton and Central Nervous System in Young Animals in Vitamin A Deficiency. Drs. S. B. Wolbach and O. A. Bessey.

BOSTON LYING-IN HOSPITAL

There will be a meeting of the Journal Club of the Boston Lying-in Hospital on Wednesday, January 15, at 8:15 p.m. Dr. Richard D. Bryant, of the Department of Obstetrics, Cincinnati General Hospital, will speak on "Treatment of Eclampsia by Veratrum Viride."

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will rehearse under Alexander Thiede, formerly concertmaster of the Cleveland Symphony Orchestra, every Thursday at 8:30 p.m. Those interested in becoming members should communicate with Dr. Julius Loman, Pelham Hall Hotel, Brookline (BEA 2430).

JEWISH MEMORIAL HOSPITAL

A meeting of the staff of the Jewish Memorial Hospital will take place on Thursday, January 16, in the hospital auditorium, 45 Townsend Street, Roxbury, at 8:30 p.m. Dr. Samuel A. Levine will speak on "Some Important Errors in the Diagnosis of Heart Disease."

All interested physicians are cordially invited to attend.

HARVARD MEDICAL SOCIETY

There will be a meeting of the Harvard Medical Society on Tuesday, January 14, in the amphitheater of the Peter Bent Brigham Hospital at 8:15 p.m. Dr. A. Rosenblueth will speak on "A Physiological Analysis of Abnormal Neuromuscular Function."

CUTTER LECTURE

Dr. Henrik Dam, associate professor at the Biological Institute, University of Copenhagen, will give the Cutter Lecture on Preventive Medicine at the Harvard Medical School on Thursday, January 30. His subject will be "Vitamin K: Its general significance in biochemistry, and its role in human pathology and its application in therapeutics," and the lecture will begin at five o'clock in the amphitheater of Building E. These lectures have been given annually since 1912. The medical profession, medical and public health students and others interested are invited to attend.

NEW ENGLAND WOMEN'S MEDICAL SOCIETY

The annual meeting of the New England Women's Medical Society will be held at the Myles Standish Hotel on Thursday, January 16. A business meeting will be held at 6:30 p.m. followed by dinner at 7:15 p.m. Dr. Elliott P. Joslin will speak on "My Present Interest in Diabetes."

NEW ENGLAND PATHOLOGICAL SOCIETY

The next meeting of the New England Pathological Society will be held at the Beth Israel Hospital on Thursday, January 16, at 8 p.m.

PROGRAM

March Hemoglobinuria. Dr. D. R. Gilligan.

Intestinal Obstruction. Dr. Jacob Fine.

Incidence and Distribution of Coronary Artery Occlusions. Dr. M. J. Schlesinger.

Business meeting.

NEW ENGLAND HEART ASSOCIATION

The next meeting of the New England Heart Association will be held at the Peter Bent Brigham Hospital on Monday, January 27, at 8:15 p.m.

PROGRAM

Pulmonary Congestion and Edema in Heart Disease: With special reference to the interpretation of roentgenological findings. Dr. Soma Weiss.

The Picture of Shock in Heart Disease. Drs. Richard V. Ebert and E. A. Stead, Jr.

The Prognosis of Right Bundle-Branch Block. Drs. George Perera and Herman Erlanger.

Observations on the Circulation in Some Forms of Congenital Heart Disease. Drs. E. C. Eppinger, Robert E. Gross and C. Sidney Burwell.

The Effect of Flow of Blood in Small Vessels on Hematocrit Reading. Drs. E. A. Stead, Jr., and Richard V. Ebert.

The Wolff–Parkinson–White Syndrome with Attacks of Ventricular Tachycardia. Drs. S. A. Levine and Paul B. Beeson.

Interested physicians and medical students are cordially invited to attend.

VAN METER PRIZE AWARD

The American Association for the Study of Goiter again offers the Van Meter Prize Award of three hundred dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the association, which will be held at Boston, Massachusetts, on May 26, 27 and 28, provided essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words and must be presented in English; a typewritten double-spaced copy should be sent to the corresponding secretary, Dr. W. Blair Mosser, 133 Biddle Street, Kane, Pennsylvania, not later than April 1.

A place will be reserved on the program of the annual meeting for presentation of the prize-award essay by the author, if it is possible for him to attend. The essay will be published in the *Proceedings* of the Association. This will not prevent its further publication, however, in any journal selected by the author.

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Sunday, January 12

Sunday, January 12

†4 p.m. Hormones and Children. Dr. Joseph C. Aub. Free public lecture. Harvard Medical School, Building D.

†4 p.m. What About Cancer? Dr. W. Stewart Whittemore. Public health lecture. Cambridge Hospital, Margaret Jewett Hall.

Monday, January 13

12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

Tuesday, January 14

*9–10 a.m. Intestinal Intubation. Dr. Louis Zetzel. Joseph H. Pratt Diagnostic Hospital.

12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital amphitheater.

8:15 p.m. A Physiological Analysis of Abnormal Neuromuscular Function. Dr. A. Rosenblueth. Harvard Medical Society. Amphitheater, Peter Bent Brigham Hospital.

Wednesday, January 15

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12 m. Clinicopathological conference. Children's Hospital.

*2–4 p.m. Dyspnea and Cough. Drs. C. S. Burwell and Robert Gross. Peter Bent Brigham Hospital.

8:15 p.m. Treatment of Eclampsia by Veratrum Viride. Dr. Richard D. Bryant. Journal Club, Boston Lying-in Hospital.

Thursday, January 16

*8:30 a.m. Combined clinic of the medical, surgical, orthopedic and pediatric services of the Children's Hospital and the Peter Bent Brigham Hospital, at the Peter Bent Brigham Hospital.

*9–10 a.m. Chorioepithelioma. Dr. J. T. Smith. Joseph H. Pratt Diagnostic Hospital.

6:30 p.m. New England Women's Medical Society. Myles Standish Hotel, Boston.

8 p.m. New England Pathological Society. Beth Israel Hospital, Boston.

*8:15 p.m. Surgery of the Chest. Dr. Edward D. Churchill. United States Naval Hospital, Chelsea.

8:30 p.m. Some Important Errors in the Diagnosis of Heart Disease. Dr. Samuel A. Levine. Jewish Memorial Hospital.

Friday, January 17

*9–10 a.m. The Present Status of Pneumonia Therapy. Dr. Maxwell Finland. Joseph H. Pratt Diagnostic Hospital.

*8 p.m. Relation of the Internal Secretions to Cancer. Dr. Joseph C. Aub. William Harvey Society. Auditorium, Beth Israel Hospital, Boston.

Saturday, January 18

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*Open to the medical profession.

†Open to the public.

January 13, 14 — Third Annual Congress on Industrial Health. Page 999, issue of December 12.

January 21 — South End Medical Club. Page 41, issue of January 2.

January 27 — New England Heart Association. Page 87.

January 30 — Cutter Lecture. Page 87.

February 13 — Pentucket Association of Physicians. Page 263, issue of August 15.

February 20–22 — American Orthopsychiatric Association, Inc. Page 999, issue of December 12.

March 8 — American Board of Ophthalmology. Page 201, issue of August 1.

March 12–14 — New England Hospital Assembly. Hotel Statler, Boston.

April 21–25 — American College of Physicians. Page 1065, issue of June 20.

May 21, 22 — Massachusetts Medical Society, Boston.

June 2–6 — American Medical Association. Cleveland, Ohio.

District Medical Societies

ESSEX SOUTH

February 5 — Gastric and Duodenal Ulcer: Diagnosis and treatment. Dr. Arthur Allen. Lynn Hospital.

March 5 — X-ray in Heart Disease. Dr. Merrill C. Sosman. Essex Sanatorium, Middleton.

April 2 — Pediatric Problems in General Practice. Dr. Joseph Garland. Addison Gilbert Hospital, Gloucester.

May 14 — Relation of the Doctor to the Law. Mr. Leland Powers. New Ocean House, Swampscott.

FRANKLIN

January 14.

March 11.

May 13.

Meetings will be held at 11 a.m. at the Franklin County Hospital, Greenfield.

NORFOLK

January 28 — Carney Hospital.

February 25 — Medicolegal meeting. 8:30 p.m. Hotel Puritan, Boston.

March 25 — To be announced.

May 8 — Censors' meeting. Hotel Puritan.

SUFFOLK

January 29 — Page 604, issue of October 10.

April 30 — Page 604, issue of October 10.

WORCESTER

February 12 — Worcester State Hospital, Worcester.

March 12 — Memorial Hospital, Worcester.

April 9 — Hahnemann Hospital, Worcester.

Supper at 6:30 p.m. followed by a business meeting and scientific program.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Life of Sir William Osler. By Harvey Cushing, M.D. 8°, cloth, 1417 pp., with 10 illustrations. New York: Oxford University Press, 1940. $5.00.

Surgical Anatomy of the Head and Neck. By John F. Barnhill, M.D., LL.D., formerly professor of otolaryngology, Indiana University School of Medicine, emeritus professor of surgery of the head and neck, formerly chief of the Department of Head and Neck Surgery, Indiana University Hospitals, and honorary professor of anatomy, University of Southern California School of Medicine; and William J. Mellinger, M.D., associate professor of anatomy, University of Southern California School of Medicine, chief of Department of Eye, Ear, Nose and Throat, Cottage Hospital, Santa Barbara, and otolaryngologist, Santa Barbara General and St. Francis hospitals. Introduction by Paul S. McKibben, professor of anatomy, University of Southern California School of Medicine. Second edition, rearranged and revised. 4°, cloth, 773 pp., with 431 illustrations. Baltimore: Williams & Wilkins Company, 1940. $15.00.

Diagnosis and Treatment of Arthritis and Allied Disorders. By H. M. Margolis, M.D., M.S. (in med.), chief, Arthritis Service, St. Margaret Memorial Hospital, associate in medicine, Montefiore Hospital, and consultant in medicine, Pittsburgh Diagnostic Clinic. 8°, cloth, 551 pp., with 140 illustrations. New York: Paul B. Hoeber, Incorporated, 1940. $7.50.

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